DOCTOR OF PHILOSOPHY

Comorbid opioid dependence and chronic pain
Clinical implications

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Declaration

The candidate is the author of the thesis and, unless otherwise stated, all references cited have been consulted by the candidate. The work, of which the thesis is a record, has been completed by the candidate and has not been previously submitted or accepted for a higher degree.

Abstract

Context

Chronic pain and opioid dependence confer substantial individual and societal burdens and are notoriously difficult to treat effectively. Their comorbid presentation further complicates effective treatment through complex physiological and environmental interactions.

Objectives

(1) What are the clinical characteristics and treatment outcomes associated with comorbid chronic pain in ORT patients?

(2) Does the patient-attributed direction of the causal relationship in the development of opioid dependence and chronic pain identify two clinically-distinct treatment populations?

(3) What is the incidence of iatrogenic opioid dependence or abuse following opioid analgesic treatment?

(4) Is there evidence of opioid-induced hyperalgesia in humans?

Methods

Primary data

Participants were 467 treatment-seeking, opioid-dependent patients.

Materials comprised standardised instruments – focusing on illicit substance use and mental health characteristics – completed by medical staff at study inception, and extracts of routinely-collected clinical datasets spanning the follow-up period.

Procedures involved the use of a health informatics approach. Electronic linkage of data collected at study inception with routinely-collected clinical datasets spanning the 5-year follow-up period.

Secondary data

Systematic searches were undertaken using six electronic research databases, supplemented by manual searches.

Study quality was assessed using instruments developed by NIH.

Data synthesis using random effects models (DerSimonian-Laird method) generated: (1) a pooled incidence of iatrogenic dependence or abuse following opioid analgesic treatment; and (2) a pooled effect of opioid exposure on the development of opioid-induced hyperalgesia.

Additional analyses included assessment of heterogeneity in study effects, within- and between-study risk of bias and sensitivity analyses.

Results

A total of 246 (53%) patients reported comorbid chronic pain. This 'comorbid' group was associated with increased mortality, physical and mental health problems, service utilisation and

illicit drug use, specifically benzodiazepines and cannabinoids. Within the 'comorbid' group, patients who reported a causal impact of opioid dependence on the development of pain were associated with increased illicit drug use and psychiatric morbidity. Secondary data analyses revealed a 4.7% incidence estimate of iatrogenic dependence or abuse following opioid analgesic treatment, and evidence of the development of opioid-induced hyperalgesia following therapeutic opioid exposure.

Conclusions

Elevated mortality, morbidity and illicit drug use in opioid-dependent patients with comorbid chronic pain reflects a patient population with substantial health burdens. The dynamic relationship between these severe and chronic conditions necessitates complex, multimodal treatment strategies and multiagency collaboration, including general psychiatric intervention. Whilst a substantial proportion reported that opioid dependence developed as a consequence of pain problems, there is evidence to suggest that the assumed risk of iatrogenic opioid dependence and abuse may be an overestimate; however, therapeutic opioids may lead to other problems that impact on treatment effectiveness, such as opioid-induced hyperalgesia.

Chapter 1

Introduction

1.1 Context

With increasing longevity and, consequently, an aging worldwide population, chronic conditions – especially those that are associated with chronic pain – are increasingly prevalent and burdensome, both at an individual and a societal level (Vos *et al.*, 2015). Between 1997 and 2002, the use of opioids, such as oxycodone and fentanyl, increased in the US by at least 200% in the control of chronic, non-cancer pain (Gilson *et al.,* 2004). Increasing use of prescription opioids was associated with a corresponding proportional increase in abuse of opioids, such as: fentanyl (around 600%); morphine (around 100%); and oxycodone (around 350%) in the US between 1997 and 2003 (Gilson *et al.,* 2004). The British Pain Society's response to the All Party Parliamentary Group on Drug Misuse Inquiry acknowledged that, whilst the UK has seen a paralleled rise in opioid analgesic prescribing in the past decade, much of the evidence in support of associations between increased prescribing and increased non-medical use of prescription opioids comes from the US (Stannard, 2013). This reported increase in use, and potential subsequent abuse, of opioids can be attributed, at least in part, to the introduction of controlled release forms of opioids that are reported to control pain for relatively longer periods (Moorman-Li *et al.*, 2012). In this present chapter, the effects of opioid use in both the treatment of chronic, non-cancer pain and in recreational users will be explored. This includes adverse effects of opioid use, factors associated with risk for opioid misuse and the clinical challenges in effectively managing comorbid chronic pain and opioid dependence or abuse.

1.2 Opioid analgesic treatment and incidence of opioid abuse in treatment-seeking patients with chronic pain

Chronic pain impacts negatively on individuals' quality of life and on the national and global economy and, in consequence, the search for sources of adequate analgesia that function in the long term is justifiable. When aiming to permanently address pain symptoms, patients and clinicians often rely on opioids for control of severe or debilitating pain. The primary aim of treating pain with opioids is initially to bring about analgesia, which subsequently results in an improvement of physical functioning and quality of life (Ballantyne and Shin, 2008). Opioids have been proven to be effective analgesics, at least in the short term and, when prescribed to

control low intensity pain at an early stage in the development of symptoms, can be effective in controlling pain in the longer term (Webster *et al.,* 2007). When prescribed for high intensity pain over a long period of time, however, this can result in an increased risk of opioid abuse (Webster *et al.,* 2007). In the short term, opioid analgesics seem, therefore, extremely effective in managing pain, especially non-cancer pain, and they are an effective analgesic (Kalso *et al.,* 2004); however, often the negative side effects of long-term opioid use are ignored. In adults over the age of 65, Reid *et al.* (2010) reported that approximately 48% of patients who used opioids to treat chronic pain stopped treatment within one year, citing extreme side effects and lack of efficacy in pain control. This finding, the cessation of treatment due to the presence of adverse side effects associated with opioid use, was also replicated by Moore and McQuay (2005) and by Papaleontiou *et al.* (2010).

The rates of opioid abuse in patients in receipt of opioid analgesic therapy have been occasionally explored in the medical literature. In 2009, opioid abuse was recorded in 2.7% of the adult population of the United States using opioids for non-medical purposes. While opioid abuse is estimated to exist in about 20% of those who use opioids to treat chronic pain (Sehgal, Manchikanti and Smith, 2012), there is also evidence to suggest that opioid abuse accounts for approximately 10% of total drug use in the United States (Hojsted and Sjorgren, 2006). Non-therapeutic use of opioids could account for as many as 11.6 of every 1000 deaths in the United States (Manchikanti and Singh, 2008). In addition, more adults have taken part in the recreational use of opioids than of other illicit drugs, like marijuana (Denisco, Chandler and Compton, 2012). Not only has the illicit use of opioids seen an increase, but the average dose has seen a surge from approximately 70 morphine-equivalent (ME) mg/person/day to approximately 350 ME mg/person/day (Manchikanti and Singh, 2008). Whilst these findings have been extracted from studies that examined individuals using opioids over time, many of these statistics may only be conservative estimates, as many opioid abusers do so clandestinely, without being detected by medical professionals or being included in population or large-scale studies (Edlund *et al.*, 2010). Whilst recent statistics concerning opioid nonmedical use and abuse are not available in large populations, the steadily increasing percentage of opioid abuse can possibly point to a growing problem among adults who use opioids for therapeutic purposes, as well as for recreational use.

1.3 Therapeutic and recreational use of opioids, and characteristics associated with risk of opioid abuse

1.3.1 The role of neurobiology in liking of opioids

Many individual and environmental factors influence whether opioid abuse develops following therapeutic or recreational exposure. The neurobiological effects of opioids underpin many of these factors, in consequence of the intense feelings of pleasure associated with opioid drugs. A succinct overview of the neurobiological mechanisms underlying opioid liking was given by Kosten and George (2002). Opioids enter the brain through the bloodstream and attach to mu opioid receptors on the surfaces of opioid-sensitive neurons. Activation of these receptors triggers the same biochemical processes that 'reward' people with the pleasurable feelings associated with behaviours that promote basic life functions, such as eating and sex. The mesolimbic 'reward' pathway is one of the neural circuits activated by opioids. Signals generated in the ventral tegmental area (VTA) cause a release of dopamine (DA) in the nucleus accumbens (NAc). The release of DA into the NAc results in intense feelings of pleasure. Lasting memories are created in other parts of the brain, associating these pleasurable feelings with the people, circumstances and environmental context present during opioid exposure. These memories, known as 'conditioned associations', then result in drug cravings in the presence of environmental cues. Whilst recreational or analgesic exposure to opioids is essential to experiencing opioid liking, a number of factors are likely to determine whether individuals continue to use opioids for a sufficient duration to develop dependence or abuse disorders.

1.3.2 Association of opioid abuse with therapeutic analgesic treatment for chronic pain

The use of opioids to treat chronic pain is steadily increasing and subsequently so is the increasing possibility of physical opioid dependence. Whilst the development of acute dependence is considered to be a normal reaction to opioid analgesic exposure, the development of chronic dependence or abuse is considered to be an aberration (Prater *et al.*, 2002). The development of opioid dependence and abuse disorders following therapeutic opioid exposure is generally considered to be an iatrogenic syndrome, a phenomenon commonly referred to as 'iatrogenic addiction to opioids' (IAO). Opioid dependence and abuse disorders are characterised by the compulsive use of opioids despite associations with negative physical, economic, social, and emotional consequences (Jovey *et al.,* 2003). Passik *et al.* (2003) further suggested that, whilst in the case of heroin addiction, dependence and tolerance are defining characteristics, dependence may not be the sole outcome of interest in iatrogenic populations, and that non-prescribed patterns of use, or other types of abuse, should also be

considered. Among those who have access to prescription drugs for chronic pain, as many as 9% of individuals using opioids could be abusing them for non-therapeutic purposes (Manchikanti *et al.,* 2006b). One of the principal reasons that opioids are abused is due to the sense of pleasure or euphoria they induce, especially as newer opioids, available through prescription, induce an extended sense of euphoria due to the controlled release of chemicals (Sehgal, Manchikanti and Smith, 2012). Opioids are also used in addition to other substances, like alcohol or benzodiazepines, to enhance the euphoric effect (Simoni-Wastila, Ritter and Strickler, 2004). Manchikanti *et al.* (2011) reported that opioid abuse was found in, on average, about 15% of patients with pain who did not have comorbid substance abuse issues, while this rate escalated to about 35% in those who had a history of substance abuse. Moreover, such abuse has most often been found in individuals who use higher doses of prescribed opioids than lower doses (Lee *et al.,* 2011). In individuals who need to use analgesic opioids for long term, non-malignant pain management, Silverman (2009) argues there needs to be a concerted effort to minimise the risk of opioid abuse associated with chronic exposure. Ballantyne and Shin (2008) reported that individuals treated with opioids for control of chronic pain and individuals who are abusing opioids can be difficult to distinguish. Opioid abuse can result in psychological responses/cravings or physical dependence. Psychological responses are manifested in emotional responses such as dysphoria and cravings on withdrawal, while physical dependence is evidenced by characteristics such as diarrhoea, tremors, hyperhidrosis and sleeplessness (Ballantyne and Shin, 2008). In those dependent on opioids, about 17% of males and 19% of females engaged in 'doctor shopping' – making frequent visits to clinics to obtain additional opioid prescriptions (Webster and Webster, 2005). Several studies reported that, despite the short term effectiveness of opioids to control pain, opioid use induces adverse side effects in the long term, and can lead to opioid abuse and increased pain sensitivity over an extended period of time (Kalso *et al.,* 2004; Ballantyne, 2007).

1.3.3 Demographic and individual characteristics associated with opioid abuse

It has been observed in numerous studies that various factors can be precursors to opioid abuse among adults. These factors include physical demographics, social characteristics, concurrent comorbidities, and genetic predisposition for substance abuse (Sehgal *et al.*, 2012). Ballantyne (2007) suggested that it is the presence of psychosocial, drug related and physical factors together that point to the risk of opioid abuse. This section provides an overview of the factors that may be indicators of risk for opioid abuse.

1.3.3.1 Physical demographics

Sehgal *et al.* (2012) stated, in their review, that many of those who abuse opioids are found to live in 'rural, suburban and small urban areas' as opposed to large urban cities. Cicero *et al.* (2007) indicated, in a study of suburban and rural area opioid use, that, while a larger proportion of individuals residing in suburban areas used prescription opioids for therapeutic analgesia, there was also a larger proportion who abused opioids in these areas. This indicates that, in areas where a large number of opioids are prescribed for therapeutic use, there is also a greater potential for abuse present (Cicero *et al.,* 2007). In addition to increased availability, and at relatively low cost, in rural areas, the nonmedical use of prescription opioids may be considered more socially acceptable than the use of illicit drugs like heroin (Cicero *et al.,* 2007). Certain markers of deprivation status were also found to be consistently associated with opioid abuse. Individuals who were found to have opioid abuse issues also had a low self-reported health status (Fitzcharles *et al.,* 2011), low socioeconomic status (Spiller *et al.,* 2009), and had difficulty in retaining employment (Sehgal *et al.* 2012). It is worth noting, however, that there is little evidence to support an understanding of the cause-effect relationships between these characteristics and opioid abuse.

1.3.3.2 Individual characteristics

There are demonstrated to be age associations with risk of opioid abuse. While there were found to be adults of all ages abusing opioids, the majority of them were under the age of 25 years and abuse was reported to decrease as age increased (Denisco, Chandler and Compton, 2012; Simoni-Wastila, Ritter and Strickler, 2004; Edlund *et al.,* 2010; Webster and Webster, 2005). Tetrault *et al.* (2007) reported that, among women, opioid abuse occurred later (at an average age 24 years or older) while men started abusing opioids much earlier than women. In addition, rates of opioid abuse were reported to be high during adolescence (age 12-17 years) (Manchikanti and Singh, 2008; Subramaniam and Stitzer, 2009). Adolescents may be particularly vulnerable as they may find it relatively easy to obtain prescription opioids from family or friends at no cost (Manchikanti and Singh, 2008). Subramaniam and Stitzer (2009) and Tiffany *et al.* (2012) reported that adolescents vulnerable to multiple instances of substance abuse may have psychiatric conditions such as attention deficit and hyperactivity disorder (ADHD).

Gender has a significant impact on opioid abuse, but neither males nor females have been found to be consistently associated with elevated risk. While, in Simoni-Wastila *et al.* (2004), females were shown to have more tendencies for opioid abuse, another study indicated that males were found to abuse non-treatment opioids more than females (Sehgal *et al.*, 2012). This latter finding

is significant in that no such gender bias was found among those who used opioids solely for treatment purposes (Sehgal, *et al.*, 2012).

Certain other individual characteristics were also found to be associated with opioid abuse. Tetrault *et al.* (2008) indicated that cigarette smoking amongst women, but not amongst men, may also be indicative of future non-medical use of opioids. Hooten *et al.* (2011) reported that current smokers indicated greater levels of pain and increased sensitivity to pain than former smokers or non-smokers. Females who experienced pre-adolescent sexual abuse were also reported to have a higher risk for opioid abuse and mental illness than females who were not abused as children (Webster and Webster, 2005). Other precursors of opioid abuse included the existence of a criminal record and past experiences of other substance abuse (Ives *et al.,* 2006).

1.3.3.3 Comorbidities associated with the development of opioid abuse in patients treated for chronic pain

Several conditions have been reported to exist concurrently in those who are found to abuse opioids. Comorbidities can often complicate treatment, including the delivery of effective analgesia (Gureje, 2008). Whilst, in addition to individual histories, genetic and environmental factors may be associated with the development of opioid abuse, these factors have not been specifically investigated in treatment settings to date since the appropriate depth and complexity of relevant information required would usually be unfeasible to determine during relatively short consultation sessions (Webster and Webster, 2005).

It has been observed that patients with physical conditions involving chronic pain, like arthritis or malignancies, are more likely to abuse opioids than those who do not have these conditions (Denisco, Chandler and Compton, 2012). Since this finding might be anticipated, however, much of the literature focuses on substance use history and other psychiatric conditions.

It has been shown that patients with psychiatric disorders, such as depression and anxiety, are more likely to abuse opioids than those who do not have these conditions (Denisco *et al.*, 2012). The presence of psychiatric conditions and moderate to severe chronic pain can indicate an increased risk of opioid dependence in patients exposed to chronic opioid analgesic therapy (Sehgal *et al.*, 2012; Edlund *et al.,* 2010; Wasan *et al.,* 2007; Schieffer *et al.,* 2005). The role of psychiatric conditions in opioid abuse is presently being questioned – more specifically, the cause-effect relationship that psychiatric disorders have with opioid abuse – but, to date, no definitive conclusions have been reached in the medical literature (Manchikanti and Singh,

2008). In opioid abusers with chronic pain, the presence of anxiety and depression was found to be greater than in non-abusers with chronic pain (Manchikanti *et al.*, 2007). Similarly, in opioid-dependent clinical populations treated with opioid replacement therapy (ORT), compared with patients with no pain, opioid-dependent patients with comorbid chronic pain were shown to be significantly associated with an elevated presence of depressive and anxiety disorders (Barry *et al.*, 2009; Trafton *et al.*, 2004; Dhingra *et al.*, 2013; Stevenson *et al.*, 2014; Morasco *et al.*, 2011). Gureje (2008) suggested, however, that opioid abuse may actually be the cause of anxiety symptoms, rather than the consequence.

Another strong risk factor for the development of opioid abuse in patients with chronic pain is a personal or family history of substance abuse. An indication of previous substance abuse, like heroin or alcohol, is reported to be a strong predictor of future opioid abuse as assessed by the Opioid Risk Tool (Webster and Webster, 2005). Michna *et al.* (2004) reported that a history of substance abuse in patients was a strong indication of high-risk of opioid abuse when opioids are prescribed for chronic pain treatment. Patients using opioids for analgesia, who had a history of substance abuse, reported more pain symptoms, greater intensity of pain, and more distress from chronic pain (Passik *et al.*, 2006). The presence of substance abuse, including alcohol, even in family history, was shown to be a strong indicator of a future opioid abuse risk, even if the patients themselves had not abused any substances in the past (Webster and Webster, 2005). Excluding individuals with chronic pain from prescription opioids due to their medical or family history, however, may deny them effective pain relief (Savage *et al.*, 2008).

Wu *et al.* (2006) explored tests, like the Addiction Behaviours Checklist (ABC), that could be used by health professionals to examine current addictive behaviours in patients, and possibly predict their response to chronic opioid treatment. Whilst similar characteristics and behaviours are reported in post-abuse studies, it can be difficult to identify risk factors of opioid abuse using self-report instruments (such as the 4-item CAGE questionnaire and the Medical Outcome Study Short Form 36 (SF-36)) prior to opioid prescribing (Webster and Webster, 2005).

1.4 Social and clinical outcomes and healthcare costs associated with therapeutic and non-therapeutic use of opioids

Opioids remain the most frequently-prescribed drug class by physicians for chronic pain (Manchikanti *et al.,* 2011). The primary goal of treatment with opioids is to relieve pain, as well as to improve an individual's quality of life (Hojsted and Sjorgren, 2006). Although their efficacy has been proven for intermediate term use (8-70 days), their long-term (greater than 70 days)

and short-term (0-7 days) efficacy remains uncertain (Manchikanti *et al.*, 2011). Most studies that examine quality of life metrics during chronic opioid analgesic treatment are short-term studies and do not follow individuals in the longer term. Compared to placebos or NSAIDs, however, opioids have shown a superior capacity for controlling pain levels, but are not consistently associated with improvements in overall quality of life during chronic exposure (Furlan *et al.,* 2006).

1.4.1 Measures of health-related quality of life (HRQoL) in patients treated with opioid analgesics

With improvements in physical function being one of the major aims of therapeutic opioid use, Manchikanti *et al.* (2011) suggest that this goal is met with opioid use, since individuals who use opioids for chronic pain report an improvement in physical function. In examining driving ability, Manchikanti *et al.* (2011) reported that there was no negative impact of opioid use on psychomotor skills or other physical functions. Strassels (2008) reported that there might be some adverse effects of analgesic opioid use on patients, such as an increased reaction time and an inaccuracy of response, but also reported that there was no change in overall HRQoL and motor function measures. Ballantyne and Shin (2008) point out that, while various studies are astute in examining the ability to perform certain important physical tasks, rarely do they examine overall general HRQoL - a measure that may be as diverse as the individuals who are treated with opioids. Furthermore, most studies examine only the short-term effects of opioids on physical functioning and rarely consider long term evaluation of the wider concept of HRQoL (Ballantyne and Shin, 2008).

Chronic opioid use is associated with a number of adverse side effects, which can negatively impact on an individual's quality of life. These side effects include nausea, respiratory depression, sexual dysfunction and vomiting, amongst others (Manchikanti *et al.,* 2011). Ballantyne and Mao (2003) reported that the long term use of opioids can have a negative influence on hormone production. Long term opioid use, especially that of morphine, can lead to a decline in the body's production of cortisol, testosterone, estrogen, and follicle stimulating hormones (FSH) which can have a negative effect on an individual's quality of life by affecting menstrual cycle and sexual drive, among other things (Ballantyne and Mao, 2003). There have also been documented cases of hypogonadism in males who are in receipt of opioids for the treatment of chronic pain (specifically, long-term morphine use) along with decreased testosterone levels and sexual dysfunction (Rajagopal *et al.,* 2004). The use of opioids can ultimately lead to death - when used in large doses for long periods of time the risk of overdose, and, ultimately, death, is high (Sehgal *et al.*, 2012). A high rate of deaths related to chronic

opioid use is also exacerbated by the immunosuppressive properties of some opioids like morphine (Ballantyne and Mao, 2003). This can include inhibition of antibody production, phagocyte activity and other negative effects on immunity, resulting in a subsequent reduction in resistance to infections that can result in mortality (Ricardo *et al.*, 2004; Ballantyne, 2007).

Eriksen *et al.* (2005) reported that, regarding self-reported HRQoL, chronic exposure to opioids for chronic conditions was associated with loss of employment, a negative impact on HRQoL, and an increased use of the healthcare system. In fact, their HRQoL was poorer than that of individuals with chronic pain who were not treated with opioids, as well as those without a pain disorder. Furthermore, decreased HRQoL was also associated with moderate to severe pain levels despite use of opioid analgesics (Eriksen *et al.,* 2005). In a systematic review of the effectiveness and risk associated with chronic opioid analgesic treatment, however, Chou *et al.* (2015) reported consistent evidence of increased risk of serious harms associated with increasing opioid analgesic doses. Conversely, Maier *et al.* (2005) reported that improved HRQoL was associated with therapeutic opioid dose increases; however, they reported a loss of analgesic efficacy over a three-year period.

Another aspect that determines HRQoL is mental function. Despite the relatively positive effect of opioids on physical function, Ballantyne (2007) reported that, with stable opioid doses, an individual's mental functioning can be maintained; however, opioids seem to fall short in improving mental functioning in those who use opioids for treatment of chronic pain (Manchikanti *et al.*, 2011). Ballantyne and Shin (2008) suggested that opioids may fail to help in improving patient functioning and quality of life, but may be effective in controlling pain, to varying degrees, before tolerance to opioids develops.

1.4.2 Measures of treatment outcomes in patients in receipt of opioid replacement therapy for the treatment of opioid dependence

Patients who demonstrate tolerance to opioids and withdrawal effects on cessation of opioids, and who begin to abuse opioids, may enter ORT, irrespective of whether this state developed as a consequence of therapeutic or recreational opioid use. ORT programmes focus on a range of health-related and functional outcomes but the core outcomes are considered to be retention in treatment and control over substance use (Kidd et al., 2013). These two core aims are considered to lead to decreased mortality, drug-related harm reduction, increased health and functioning, and crime reduction. There is an absence of literature comparing retention in ORT treatment in patients with and without pain; however, a number of studies have compared substance use outcomes in these patient groups.

The National Survey on Drug Use and Health, conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA), reported a point prevalence of illicit opioid use in the US of around 2% with heroin use reported in around 0.1% of the population. Studies reveal much higher rates of illicit opioid use among people with chronic pain of around 26-32% (Sehgal et al., 2012; Ives et al., 2006), and higher ORT opioid doses in these comorbid populations compared with patients with no pain (Peles *et al.* 2005; Jamison *et al.*, 2000). Despite the high prevalence of chronic pain in patients receiving ORT (Rosenblum *et al.*, 2003), there is a relatively sparse literature comparing illicit substance use in these comorbid populations with patients in receipt of ORT who have no pain. Furthermore, most of the studies examining this issue undertake cross-sectional assessments or evaluate treatment outcomes during relatively short-term follow-up periods.

In an examination of data from the Drug Abuse Treatment Outcome Study (DATOS), Sharpe Potter *et al.* (2008) reported on substance misuse outcomes in patients on entry to treatment for substance use disorders. They included 7876 participants from within four treatment modalities: long-term residential; short-term inpatient; outpatient methadone treatment; and outpatient drug-free. Compared with the group with no pain, a significantly higher proportion of the group with moderate or severe pain reported illicit use of heroin (27% vs 14%) and nonmedical use of opioid analgesics (11% vs 4%) on at least a weekly basis. There was no group association with illicit cannabinoid use and subgroup analyses by treatment modality were not undertaken.

In a cross-sectional analysis, Barry *et al.* (2009) compared illicit substance use in 150 methadone-maintained patients with and without clinically-significant pain (CSP). CSP was defined as pain having persisted for at least 6 months with moderate-severe intensity or significant pain interference. The control group reported no pain in the 7 days preceding assessment. The most commonly-reported substance misuse concerned illicit use of cocaine (25%), cannabinoids (11%), heroin (11%), and nonmedical use of benzodiazepines (11%); however, there were no significant group differences. In another cross-sectional study, examining correlates of pain in 489 methadone-maintained patients, urinalyses were used to determine illicit substance use. Just over half of the entire cohort (58%) generated positive screen results for any substances. Similar to the finding of Barry et al. (2009), there were no significant group findings, based on the presence/absence of clinically-significant pain, for any illicit substance use or for specific substances. The pain group was, however, associated with a significantly higher therapeutic methadone dose.

In an attempt to add clarity to inconsistent findings, Dennis *et al.* (2015) undertook a systematic review and meta-analysis of the impact of chronic pain on illicit drug use in patients with opioid use disorders. They reviewed 3540 articles and selected 14 for inclusion, yielding a combined sample of 3128 patients. They examined two outcome variables: illicit opioid use; and illicit non-opioid substance use. The majority of the included studies employed the use of urinalysis to identify illicit substance use, whilst a smaller proportion relied on patient reports. As a consequence of heterogeneity in the methods used to assess outcome measures, most studies were precluded from inclusion in meta-analyses. Some studies reported number of patients using illicit opioids, some reported number of days of use, and some reported percentage of positive screens. Only two studies were included in each of the two meta-analyses; therefore, the reliability of the pooled estimates is questionable. There was no significant difference in illicit opioid use by presence or absence of pain. At least one positive urine test was used to indicate illicit opioid use; however, the potential for false-positive results has been reliably demonstrated (Keary *et al.*, 2012). In consequence, it may be wise to use a more robust means of detecting illicit opioid use, such as identification of more than one positive result within a specified period of time or number of tests undertaken, or to establish a critical percentage threshold of positive results. Pain was shown to be protective against illicit non-opioid illicit substance use. This outcome variable included data pertaining to any non-opioid illicit drug. There is evidence to suggest that opioid dependent patients with comorbid chronic pain may not be associated, uniformly, with illicit use of all non-opioid substances – for example, there may be a substantial difference in risk for benzodiazepine use compared with cannabinoid use (e.g. Ilgen *et al.*, 2006) – and, therefore, the synthesis of all illicit non-opioid substance use may be of little meaning and utility. Whilst the aims of Dennis and colleagues, in conducting this review, may be laudable, it is clear that there are insufficient homogenous studies currently available to clarify the impact of chronic pain on illicit substance misuse in patients with opioid use disorders.

Whilst gaining a cross-sectional understanding of illicit substance use on entry to treatment is of some clinical relevance, examining response to ORT treatment in the longer term, is of key importance to policy development and effective healthcare delivery. Caldeiro *et al.* (2008) examined treatment outcomes at 12-month follow-up of 582 patients in a Veterans Affairs (VA) outpatient addiction treatment facility. Assessment of pain characteristics in the cohort resulted in the identification of three groups: low pain (n=114); intermittent pain (n=275); and persistent pain (n=193). The proportion of abstinence from illicit drug use was similar across all three groups at baseline; however, the group with persistent pain was associated with poorer

outcomes at 12-month follow-up. There was a significant stepwise relationship between pain group and abstinence at follow-up, with the highest proportion of abstinence found in the 'low pain' group (58%) and the lowest proportion found in the 'persistent pain' group (44%).

A further concern in treatment-seeking, opioid-dependent populations is the extent of problematic substance use – the amount of drug consumption, duration of drug use and frequency of drug use. Trafton and colleagues (2004) examined frequency and duration of illicit substance use in a sample of 251 veterans attending eight ORT treatment facilities who were in receipt of either methadone or levo-alpha-acetyl-methadol (LAAM). They reported that, on entry to treatment, patients with pain had used illicit substances more frequently than patients with no pain in the preceding 30 days and for longer durations during their lifetimes. This finding related specifically to substances associated with potential analgesic effects. Increased frequency of illicit opioid used was noted in patients with pain in the preceding 30 days (2.3 versus 0.8 days in patients with no pain) and increased duration during their lifetimes (2.9 versus 0.9 years in patients with no pain). Increased frequency of illicit cannabinoid use was noted in patients with pain in the preceding 30 days (2.8 versus 0.8 days in patients with no pain) and increased duration during their lifetimes (10.3 versus 7.5 years in patients with no pain). Increased duration of nonmedical sedative use during their lifetimes was noted in patients with pain (2.5 versus 0.4 years in patients with no pain). There were no group associations with alcohol, cocaine, heroin or poly-substance use. Information concerning duration of pain symptoms were not available; therefore, one limitation of the study was that the authors were unable to distinguish between chronic and acute pain on entry to treatment.

At 12-month follow-up of the aforementioned study by Trafton and colleagues, Ilgen *et al.* (2006) reported a high attrition rate (20%, n=51) primarily due to participants being 'unreachable', but also due to incarceration or death. A repeated measures analysis of 30-day, self-reported illicit drug use indicated an overall effect of time whereby significant decreases were associated with all substances excepting cannabinoids (which were associated with a very marginal increase over time). There were significant group and interaction effects reported for illicit opioid use with greatest overall use and greatest reduction over time shown in the pain group. The final significant finding was an effect of group for cannabinoid use whereby the pain group was associated with overall elevated use. In addition to the inability to distinguish between acute and chronic pain at baseline and indications that the relatively high attrition rate was largely associated with 'harder to reach' populations, this study also failed to corroborate self-report measures with immunoassay testing.

Selection of the method(s) used to detect illicit substance use in opioid-dependents should be of key concern in studies. Detection of substance misuse is typically undertaken through immunoassay-based testing of urine samples and through patient self-reports. Self-report measures are frequently criticised in the literature and generally regarded as unreliable (e.g. Pesce, 2012); however, immunoassay-based testing has also been demonstrated to be unreliable to some degree (e.g. Schwartz *et al.*, 1991; Darragh *et al.*, 2014). Furthermore, whilst urinalysis identifies the presence or absence of a substance, self-report measures can elucidate on additional information such as amount and pattern of use or route of administration. Frequently in research studies, self-report data are discarded in favour immunoassay findings; however, the two types of data may be complementary – either as corroboration of one another or, through triangulation, may provide a more complete profile of substance use.

1.4.3 Healthcare and societal costs associated with opioid abuse

Opioid abuse has a significant impact on medical costs. These costs are not simply a reflection of treatment for opioid abuse, but also include treatment for the sequelae of abuse. The National Institute on Drug Abuse highlights a range of medical morbidities that arise as a consequence of opioid abuse, and they include disorders of the cardiovascular, respiratory, gastrointestinal and neurological systems (NIDA, 2017). In the United States, the annual medical costs for those who abuse opioids is approximately $16,000 compared to $1,800 for those that do not abuse opioids but are in receipt of an opioid prescription (Sehgal *et al.*, 2012; Strassels, 2009). Similar statistics are not available, however, for the UK.

In the short term, while analgesic opioids may seem to decrease individual dependence on the healthcare system, chronic opioid use may result in health issues in the longer term that may include mental illness, particularly affective disorders, which may subsequently increase individual dependence on primary and secondary health services (Jensen *et al.*, 2006). While most opioid therapies may be used to lessen the burden of care on the health system, reduce pain and improve HRQoL, management of opioid therapies and their adverse effects may actually increase the burden of care on the physician and the healthcare system as a whole - with an increased demand on the time of health professionals and clinic personnel (Ballantyne and Mao, 2003).

In addition to the economic burden placed on the healthcare system by chronic therapeutic opioid use, opioid abuse can also be an economic burden on the society as a whole, including the cost of lost productivity and criminal justice system costs related to opioid abuse (Strassels, 2009). Sehgal *et al.* (2012) stated that individuals who abused opioids missed approximately

two days of work per month due to their habit, whilst those that were not opioid-dependent missed less than one day of work per month (Sehgal *et al.*, 2012; Eriksen *et al.,* 2005). In addition, the use of opioid analgesics during an injury may also prevent individuals from returning to their job effectively and ultimately contribute to professional disability (Manchikanti and Singh, 2008; Kidner *et al.*, 2009). Long-term opioid analgesic use was associated not only with an inability to work, but also an increase in self-reported loss of function and a decline in HRQoL (Manchikanti and Singh, 2008). This is particularly true of individuals who manage chronic pain for work related injuries rather than other chronic conditions (Kidner *et al.*, 2009).

1.5 Clinical challenges in effective management of comorbid chronic pain and opioid dependence

1.5.1 Disease trajectories in the comorbid presentation of chronic pain and opioid dependence

As discussed, chronic pain is a highly prevalent comorbidity in patients in receipt of ORT for the treatment of opioid dependence. Several disease trajectories may contribute to the development of this comorbid presentation. First, iatrogenic opioid abuse may develop in patients with chronic pain exposed to opioid analgesic treatment. Secondly, where pain is poorly managed, patients with persistent pain may turn to illicit or nonmedical substance use in attempts to control their pain – a phenomenon commonly referred to as 'pseudoaddiction'. Thirdly, opioid-induced hyperalgesia (OIH), a paradoxical increase in pain sensitivity following opioid exposure, may cause the development of pain, exacerbate chronic pain or prolong acute pain in patients in receipt of ORT for the treatment of opioid dependence. Fourthly, opioid-dependent patients are associated with increased risk of pain, both from accidental injury as a function of poor coordination resulting from the sedating effects of high-dose opioids (Buckeridge *et al.*, 2010) and from greater exposure to situations that result in physical trauma, violence and injury (NIDA, 2017). Indeed, in an evaluation of the impact of massage on chronic pain in opioid-dependent patients in receipt of ORT, Wiest *et al.* (2015) reported that pain had developed in more than three quarters of opioid-dependent patients as a consequence of some type of physical injury, including motor vehicle accidents, accidents/falls and partner abuse.

The issues of iatrogenic opioid abuse, pseudoaddiction and OIH necessarily impact on the development of treatment strategies and the effectiveness of therapeutic interventions. These three issues will be addressed further in this section.

1.5.2 Iatrogenic opioid dependence and abuse

The prevalence and incidence of chronic, relapsing conditions have implications for policy development, resource allocation and healthcare delivery. Chronic pain is notably difficult to treat effectively, in part, due to the debilitating side effects associated with medicinal treatments. The effective use of opioids to treat acute pain or malignant disease is well-accepted; however, their use in the treatment of chronic pain remains controversial (Benyamin, 2008). In the absence of effective treatment strategies for chronic pain, many physicians turn to the use of long-term opioid analgesic therapy, in spite of potentially significant side effects. Common side effects of chronic administration include sedation, dizziness, nausea and vomiting, constipation, respiratory depression, tolerance and physical dependence. The risk of physical dependence and abuse associated with opioids is a major clinical concern that may deter adequate analgesic prescribing for patients whose previous treatment regimens have proven unsuccessful (Jamison *et al.*, 2011). To ensure that patients are not denied treatment unnecessarily, there is a need for quantification of the risk of opioid dependence or abuse as a consequence of analgesic treatment.

Within this domain of study there are several terms that are used in an ill-defined way or even used interchangeably, and this further complicates issues that are already abstruse and that require to be addressed using precision and clarity. Illicit drug use is indicated by the use of such terms as 'abuse', 'addiction', 'misuse', 'dependence', and so on. Expert guidance provides varying definitions that, in addition, have changed over time. The medical literature draws on different sources of definitions or uses these terms without defining their use. The term 'addiction' is ubiquitous in the literature; however, in many instances, its use is ambiguous and not well-defined. In some of the literature it is used to indicate a clinical disorder but, in much of the literature, it is used as an 'umbrella' term to encapsulate concepts such as drug misuse and aberrant drug-related behaviour. It is pertinent to note that the term 'addiction' is no longer used in the International Classification of Diseases (ICD) nor in the Diagnostic and Statistical Manual (DSM).

Several reviews have examined the relationship between opioid analgesic prescribing and opioid misuse; however, many examined prevalence (existing cases) – rather than incidence (new cases) – and, in consequence, were unable to conclude that dependence or abuse was a function of opioid analgesic exposure. In addition, many used the wider outcomes of 'addiction', 'drug misuse' or 'aberrant drug-related behaviour' – not necessarily indicating problematic substance use, since these concepts include recreational use and other forms of non-problematic use. Furthermore, since most studies included in these reviews were unable to control for pre-

existing drug problems, findings may reflect prevalence – rather than incidence – and, therefore, may not indicate an iatrogenic syndrome.

1.5.2.1 Limitations of previous reviews

Littlejohn *et al.* (2004) reviewed the literature systematically and addressed four questions, the second of which is of relevance here:

1. Are opioids effective in the treatment of chronic non-malignant pain?
2. If so, do the risks of iatrogenic addiction outweigh the benefits?
3. To what extent do patients with primary opioid addiction experience chronic pain?
4. How should this pain be treated?

They restricted their searches to the preceding 10 years arguing that literature that had 'stood the test of time' would continue to be cited; presumably suggesting that these papers would be identified in manual searches of the references of included papers. They did not indicate, however, if these manual searches were undertaken. They identified 555 publications and included 102 articles– of which 34 reported primary data analyses and 68 were reviews or expert opinions. Of these 102 articles, 92 dealt with opioid treatment in patients with chronic non-cancer pain (CNCP) and 10 dealt with patients with chronic pain who were receiving primary treatment for opioid dependence.

They concluded that discussion of the addictive potential of opioids was found principally in reviews and expert guidance for clinicians but they did attempt to quantify this issue using the primary data analyses available to them. The authors of this review did differentiate between opioid abuse and opioid dependence. They reported on 7 primary data studies which addressed the second of their four review questions. These studies reported between 0% (addiction) / 0% (withdrawal) and 24% (dependence) / 27% (addiction) / 41% (abuse). It was not made clear, however, how these study authors defined the varied terms that they used. Furthermore, the authors of this review discussed prevalence rather than incidence rates, therefore, failing to demonstrate that opioid analgesic exposure preceded abuse or dependence.

Noble *et al.* (2010) undertook a Cochrane review to assess the safety, efficacy and effectiveness of chronic opioid analgesic therapy for the treatment of CNCP. Whilst the authors intended to synthesise quantitative data concerning addiction, abuse and dependence rates, they reported that heterogeneity precluded this. This was largely due to the variability in thresholds for reporting adverse events and inconsistent use of definitions of events/effects. Since efficacy was a primary concern of their review, the authors necessarily restricted included studies to randomised controlled trials and pre-post case-series studies with more than 10 participants.

The total 'event' rate (assumed to be incidence), based on DSM-IV criteria, among the 9 studies in which a history of substance misuse was recorded, was 0.27%. The review authors assumed no history of substance misuse in the remaining 18 studies, arguing that a characteristic of such significance would be recorded if present, and reported a total event rate of 0.14%.

Fishbain *et al.* (2008) undertook a structured evidence-based review of the development of abuse/addiction and aberrant drug-related behaviour (ADRB) in CNCP patients exposed to chronic opioid analgesic therapy. Initial searches included publications up to 2006 and identified 79 articles. Studies were excluded if they did not meet inclusion criteria or where the quality assessment score fell below 65%; this resulted in the retention of 67 articles included in the review. The review authors categorised patient outcomes as having developed abuse/addiction; ADRB; or alcohol/illicit drug use determined by urine toxicology. The abuse/addiction grouping included 24 articles (2507 patients) with a pooled estimate of 3.27%. The pooled estimate of studies that excluded patients with current or prior illicit substance use (n=4, 17% of articles in this grouping) was 0.19%. Rates were substantially higher in both the ADRB group (11.5% and 0.59% in patients with no current or prior substance use) and the urinalysis group (14.5%).

The quality assessment threshold for included articles (65%) was set arbitrarily and is higher than the conventionally-used 50%, thereby ensuring the inclusion of high quality articles and minimising the risk of bias in pooled estimates. The term 'abuse' was used in 9 articles (38%), the term 'addiction' was used in 12 articles (50%) and other terms (such as 'psychological dependence' or 'drug problem') were used in 6 articles (25%). It is unclear whether the term 'addiction' indicates a clinical disorder or was used in its wider sense; however, this may not have been defined in the original articles. Given the other terms used in this grouping, it appears to focus on misuse rather than on a clinical disorder. Furthermore, the searches were undertaken more than 10 years ago and, therefore, this review does not include literature from within the past decade.

Minozzi *et al.* (2013a) undertook a systematic review of the incidence and prevalence of opioid dependence in patients with and without a history of substance misuse. Incidence rates of 0-24% (median=0.5%) and prevalence rates of 0-31% (median=4.5%) were identified. A total of 2871 articles were identified up to 2011 and 135 underwent full text review. Qualitative synthesis was undertaken with 21 articles and quantitative data were extracted from 17 studies (a total of 88,235 participants). Meta-analyses were planned but not undertaken due to high heterogeneity. Two studies focused on malignant pain, 1 study included patients with a previous history of dependence and 1 study focused on acute pain whereby the duration of opioid

exposure was for 3 days and was only extended in patients whose pain continued beyond this period. Three systematic reviews were included in this review although there was no indication if this resulted in the inclusion of duplicated findings. These 3 systematic reviews were included initially although one had a low quality assessment and high risk of bias score (Littlejohn *et al.*, 2004). It was excluded only at the data extraction stage because it was not clear if the data referred to incidence or prevalence rates. Furthermore, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system of quality analysis, they determined a very low quality of evidence across studies; however, no studies were excluded at this stage.

In a subsequent publication (Minozzi *et al.*, 2013b) the authors criticised their review arguing that articles were included which were not pertinent to the question addressed in the review and which did not meet inclusion criteria. They further argued that, generally, most articles did not contain adequate information to enable quality assessment and that the approach taken in systematic reviews is unsuitable for responding to this research question because adequate research does not currently exist. It could be argued, however, that more narrowly-defined inclusion criteria and strict adherence to these criteria may have facilitated qualitative synthesis, or even meta-analysis, of a more homogenous collection of studies.

Vowles *et al.* (2015) undertook a review of problematic opioid use in patients with chronic pain; however, they did not specify if malignant pain was included or excluded and, if included, they did not synthesise data separately for these subgroups. Classification of problematic opioid use was based on consensus statements developed by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) and the Analgesic, Anesthetic and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks (ACTTION); neither of which could be considered to be indicative of diagnostic status:

1. **Misuse**: Opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects;
2. **Abuse**: Intentional use of the opioid for a nonmedical purpose, such as euphoria or altering one's state of consciousness;
3. **Addiction**: Pattern of continued use with experience of, or demonstrated potential for, harm (e.g. impaired control over drug use, compulsive use, continued use despite harm and craving).

Search dates spanned January 2000 to November 2013; a total of 366 articles were identified (320 of which were empirical studies) and, following eligibility review, 38 articles were retained for data synthesis. The rationale for exclusion of studies published prior to 2000 was not

explained. Current prevalence rates were examined and lifetime prevalence rates were excluded from the review; however, a direct causal relationship between opioid prescribing and opioid misuse cannot be assumed in the examination of prevalence, rather than incidence, since it cannot be demonstrated that opioid prescribing preceded opioid misuse.

Only one study reported an abuse rate (8%) whilst rates of misuse ranged from 0.08-81% and rates of addiction ranged from 0.7-34.1%. Some included studies provided a single rate of misuse/addiction whilst others reported a range. To ensure synthesis of the full complement of studies, the authors of this review calculated both a minimum and a maximum rate and, where a single value was reported in studies, this value was used to represent both the minimum and the maximum. Rates of misuse, weighted by sample size, were 69.4% and 69.5%, respectively. Weighted rates of addiction were 4.3% and 4.7%, respectively. Of particular note, addiction rates were lower in studies that identified prevalence assessment as a primary, rather than secondary, objective.

1.5.2.2 The need for further empirical evidence

Whilst the physiological characteristics of acute dependence are anticipated following prolonged exposure to opioids, clinical diagnoses of opioid dependence or abuse disorders are aberrations that confer substantial additional individual health burdens and further complicate treatment. Evidence suggests that physicians may be reluctant to prescribe opioids in the longer term due to the risk of iatrogenic dependence or abuse. To ensure that patients are not denied treatment unnecessarily, there is a need for quantification of the risk of opioid dependence or abuse as a consequence of analgesic treatment. Whilst a number of reviews have attempted to synthesise evidence in this area, they have focused on prevalence – rather than incidence – and, therefore, cannot infer a causal relationship between opioid analgesic treatment and dependence or abuse.

1.5.3 Pseudoaddiction

Pseudoaddiction is another phenomenon that may account for a proportion of the substance misuse reported in patients with chronic pain. The term 'pseudoaddiction' is used to indicate an iatrogenic syndrome rather than a clinical diagnosis. It is defined in The Concise Dictionary of Modern Medicine (Segen, 2012) as:

> *A drug-seeking behaviour that simulates true addiction, which occurs in patients with pain who are receiving inadequate pain medication.*

The concept first entered the literature in the late 1980s in a case report of a 17-year-old man with acute leukaemia who was admitted to hospital suffering from pneumonia (Weissman and

Haddox, 1989). He received 5mg of morphine intravenously every 4-6 hours, as required. After a few days he was reported to be exhibiting 'drug-seeking behaviours' typical of drug dependence disorder. The authors proponed that this was not an example of idiopathic drug dependence but, rather, an iatrogenic syndrome, resulting from analgesic under-treatment. Inverting the conventional use of the term 'iatrogenic', they suggested that the syndrome was a result of withholding adequate analgesia.

The term was readily-adopted by pain specialists form the early 1990s onwards in an attempt to describe patients whose drug-seeking behaviour was due to analgesic under-treatment rather than what is described in the literature as 'true addiction'. In contrast to pseudoaddiction, 'true addiction' is typically thought to be a manifestation of characteristics such as poor general, rather than specifically pain-related, psychological coping mechanisms (Elman *et al.*, 2016) and sensation-seeking behaviour in addition to impulsive personality traits (Marino et al., 2013). It is proposed that the behaviour of patients exhibiting pseudoaddiction mimics that of 'true addiction', so they may increase their dose against medical advice, lie or complain excessively to acquire more medication, engage in 'doctor shopping' or turn to street drugs in order to increase their supply. It is suggested, however, that the difference between the two is that substance misuse will cease in pseudoaddicted patients following adequate control of pain (Jamison *et al.*, 2011).

1.5.3.1 Pseudoaddiction and the limitations of diagnostic criteria for drug dependence and abuse disorders

Whilst the literature has questioned the binary addicted/non-addicted conceptualisation for almost three decades, diagnostic criteria have not evolved during this time. For example, the DSM criteria for drug dependence disorder do not address the concept of pseudoaddiction. Of the seven criteria (of which three are required for the attribution of a clinical diagnosis of drug dependence disorder), four could apply to pseudoaddicted patients. One relates to tolerance and one to withdrawal. These two criteria are not exclusive to a clinical diagnosis of drug dependence disorder since patients prescribed relatively high dose opioids for the treatment of chronic pain are likely to develop tolerance and to manifest withdrawal on removal of these opioids. Furthermore, the additional criteria, 'the substance is often taken in larger amounts than intended' and 'persistent desire to cut down', could simply indicate analgesic need. Consequently, these four criteria could result in over-inclusiveness in diagnosing drug dependence disorder and a failure to distinguish pseudoaddiction (Fishbain, 2003).

1.5.3.2 Challenging the concept of pseudoaddiction

The concept of pseudoaddiction was developed anecdotally and appears to have been accepted in the literature with little empirical validation. A systematic review of pseudoaddiction revealed 224 published articles up to the end of 2013 (Greene & Chambers, 2015). Of these 224 articles, none attempted empirical validation of the concept; 206 articles addressed pseudoaddiction as a routinely-accepted concept and 18 articles provided elaboration on the subject. Of these 18 articles, the authors of the review reported that 12 supported pseudoaddiction as a clinical syndrome, 4 argued against the phenomenon and 2 discussed it from a social perspective. Four of the papers providing support of the concept of pseudoaddiction were in receipt of pharma support; none of those that argued against the phenomenon or addressed it from a social perspective were in receipt of pharma support.

The 12 articles reported by the review authors to be in support of the concept of pseudoaddiction as a clinical syndrome primarily argued that addiction assessments, such as standardised instruments and biochemical drug screens, were not sufficiently sensitive (particularly in terms of establishing internal motivation) to discriminate between addiction and pseudoaddiction. The 4 articles refuting the concept, largely, justified their arguments based on the absence of evidence and the difficulties associated with objectively identifying internal motivation for drug-seeking behaviour. In consequence, they argued that behaviour, rather than motivation, should be used as the key diagnostic indicator. Since it is the motivation to misuse substances (i.e. to control unmanaged pain) that distinguishes pseudoaddiction from 'true addiction', it is difficult to translate this recommendation into effective clinical practice.

Whilst the review authors reported that some studies espoused and some studies refuted the concept of pseudoaddiction, despite perspective, it seems that all studies reported must conclude that there is insufficient evidence – both in terms of empirical research and diagnostic techniques – to prove or disprove the existence of the phenomenon. Whilst there is an absence of empirical evidence validating the concept of pseudoaddiction, similarly, there is no evidence to suggest that this clinically-observed and anecdotally-reported phenomenon does not exist.

1.5.3.3 Distinguishing between addiction and pseudoaddiction

Despite the assertion that pseudoaddiction could be empirically validated through the cessation of drug-seeking behaviour following adequate analgesic treatment (e.g. Savage, 2001; Weissman and Haddox, 1989), to date, there have been no prospective studies attempting to validate the concept. Opportunities for prospective validation studies may, however, be limited by physician trepidation in prescribing the required medication and doses for the treatment of

chronic pain in drug-seeking patients. Not only would concerns focus on the potential development or exacerbation of drug dependence problems, but chronic prescribing of both opioids and NSAIDs are associated with serious and debilitating side effects.

In an attempt to distinguish between 'true addiction' and pseudoaddiction on patient presentation, Elander *et al.* (2003) proposed that the presence of pain, alongside appropriate DSM criteria indicative of drug dependence disorder, should confer a classification of pseudoaddiction. This is potentially problematic, however, since it must be possible for pain and 'true addiction' to exist concurrently, in at least some patients. Numerous studies have reported a high prevalence of chronic pain in opioid-dependent clinical populations (e.g. Rosenblum *et al.*, 2003; Jamison *et al.*, 2000; Dhingra *et al.*, 2013), but it is unlikely that these comorbid populations are comprised entirely of pseudoaddicted patients. Some patients with chronic pain may be predisposed to addictive behaviour, through both intrinsic and extrinsic factors, and be referred for ORT for the treatment of 'true addiction'.

1.5.3.4 The need for further empirical evidence

It is clear that distinguishing between 'true addiction' and pseudoaddiction on patient presentation is a challenge that remains unresolved. One way in which this might be elucidated upon is to examine population differences dependent upon the relational temporal development of chronic pain and drug dependence disorder. Broadly speaking, patients who develop drug dependence disorder subsequent to chronic pain may be considered to be presenting with pseudoaddiction whilst patients whose chronic pain develops subsequent to drug dependence disorder may be considered to be presenting with 'true addiction'.

The primary limitation of this approach, however, is in reliably demonstrating the temporal relationship between the development of chronic pain and opioid dependence disorder. Reliance on patient reports of the temporal relationship between the onset of the two disorders may result in reporting bias, or it may prove difficult for patients to recall this information retrospectively. Examination of entry to respective treatment settings or initiation of respective prescribing regimens could also be misleading for a number of reasons. First, entry to ORT treatment settings is likely to occur at a much later stage in disease development compared with entry to pain management services. Secondly, entry to pain management settings or analgesic prescribing may reflect drug-seeking behaviour at a relatively early stage in the progression of drug dependence or abuse disorders rather than a genuine need for analgesic treatment. Thirdly, it is common practice for patients with substance use disorders to be treated solely in addiction services and not to be referred to other specialist services; therefore, patients

presenting with pain complaints where the general practitioner suspects possible drug-seeking behaviour may only ever be treated in addiction services. There is no obvious means of accurately identifying motives for illicit and nonmedical substance use in opioid-dependent patients with chronic pain, but a potentially-useful initial approach may be to identify the patient-attributed causal relationship between the two disorders.

1.5.4 Opioid-induced hyperalgesia

Prolonged use of opioids is associated with a number of debilitating side effects, including the potential for the development of tolerance (Volkow *et al.*, 2016), and dependence and abuse (Fishbain *et al.*, 2008). The development of OIH may represent a substantial additional challenge in the effective treatment of pain. Furthermore, it has obvious implications for the management of patients in receipt of ORT for the treatment of opioid dependence. To date, however, OIH remains relatively underexplored within clinical settings (Eisenberg *et al.*, 2015) and does not feature substantially in clinical guidelines for pain management (e.g. SIGN, 2013) or ORT (e.g. NICE, 2007).

Whilst the apparent clinical effects of opioid tolerance and OIH may be the same (i.e. increased pain), the physiological aetiologies differ and, therefore, effective management may require different approaches (Tawfic *et al.*, 2013; Bottemiller, 2012). Tolerance reflects a desensitisation of pain signalling pathways to opioids and can, therefore, be effectively treated through the escalation of opioid doses, at least in the short term. OIH reflects a sensitisation of pain signalling pathways and, in consequence, may be treated effectively by opioid rotation, reduction or cessation, as recommended in SIGN 136 (SIGN, 2013). OIH has been well-documented in preclinical studies, with the assumption that these findings can be translated to clinical settings; however, due to the cognitive components impacting on the experience of pain, these findings may not be entirely translatable (Vierck *et al.*, 2008), and the literature addressing its development in humans remains relatively sparse (Angst *et al.*, 2016).

1.5.4.1 Limitations in translating preclinical findings to clinical settings

The assessment of pain differs from the assessment of many other symptoms and illnesses in that it cannot be quantified objectively. In clinical settings, information about the presence and quality of pain is obtained from patients who have the cognitive capacity and appropriate linguistic skills to report that information. Despite this, much of the evidence for OIH comes from preclinical models, but spontaneous events such as vocalisations, sleep disruption, autonomy/over-grooming or autonomic activation may not necessarily qualify as definitive measures of pain (Vierck *et al.*, 2008). It is, therefore, questionable if pain assessment in

preclinical models measures the same phenomenon as in clinical models. The literature concerning humans is sparse and less consistent in its findings; however, clinical experience suggests that OIH is a relatively common but under-recognised phenomenon (Zylicz *et al.*, 2008). Much of the evidence concerning human populations comes from examination of patients in receipt of ORT for the treatment of opioid dependence or from populations in receipt of long-term analgesic treatment for chronic pain. These two populations are associated with very different health status, prior healthcare, current treatment regimens and opioid doses, and this may contribute to the inconsistency in clinical findings thus far.

1.5.4.2 Distinguishing between opioid tolerance and opioid-induced hyperalgesia: Implications for effective analgesic treatment

The terms 'opioid tolerance' and 'opioid-induced hyperalgesia' are often confused in the literature or used in ill-defined ways. This may be because the clinically-observable effect is the same – decreased analgesic effectiveness. They are, however, different concepts that require distinct treatment methods to ensure continued pain management (Tawfic *et al.*, 2013). In simple terms, opioid tolerance is described as a shift to the right in the dose-response curve – i.e. escalating doses are required over time to maintain the same level of analgesia. There are two prominent theories of opioid tolerance: receptor desensitisation; and receptor down-regulation (Dumas *et al.*, 2008). OIH is characterised by a downward shift whereby, paradoxically, escalating doses are associated with escalating pain sensitivity (Tompkins *et al.*, 2011). OIH is generally thought to arise following neuroplastic changes in the central and peripheral nervous systems that result in sensitisation of pronociceptive pathways; however, the exact molecular mechanisms are not well-understood (Lee *et al.*, 2011; Chu *et al.*, 2011; Younger *et al.*, 2011). Whilst there are several proposed central and peripheral mechanisms, such as alpha-2 adrenoceptors and the endocannabinoid system, the most prominent of these is considered to be the potential role of the central glutaminergic system, suggesting that opioid exposure increases N-methyl-D-aspartate (NMDA) activity. Mao *et al.* (2002) reported that prolonged morphine exposure resulted in down-regulation of spinal glutamate receptors, resulting in increased levels of glutamate available to NMDA receptors. Glutamate-associated activation of NMDA receptors can result in spinal neuron sensitisation, thereby possibly contributing to the development of OIH. It is, therefore, proposed that NMDA receptor antagonists may attenuate OIH. Indeed, this has been demonstrated in a number of clinical and preclinical studies, as discussed in several reviews (e.g. King *et al.*, 2005; Ossipov *et al.*, 2005; Mao, 2006), which further substantiates the hypothesised role of NMDA receptors in hyperalgesic states.

1.5.4.3 Dose-dependent hyperalgesic responses

Several studies, predominantly case reports, have documented hyperalgesia in response to systemic or intrathecal morphine at high doses and have reported that pain is further potentiated following dose increases (e.g. Ackerman, 2006; Axelrod *et al.*, 2007; Chung *et al.*, 2004; Mercadante *et al.*, 2005). Hooten *et al.* (2010) examined associations between opioid dose and heat pain perception in 109 patients with chronic pain undergoing opioid tapering. Heat pain perception was assessed one day following admission to the programme and on completion of opioid tapering. They reported that hyperalgesia was positively associated with baseline morphine-equivalent dose, even after adjusting for pain diagnosis, pain duration, pain severity and opioid withdrawal symptoms. There is, however, a distinct lack of evidence for OIH in lower doses. One study reported that a subset of patients, formerly addicted to opioids, experienced mild hyperalgesia at low doses but that, at higher doses, these patients experienced analgesia (Andrews, 1943). The aforementioned hyperalgesia may, however, have been an indication of inadequate analgesia (i.e. pseudoaddiction) or opioid tolerance, rather than hyperalgesia *per se,* since analgesia was attained at higher doses.

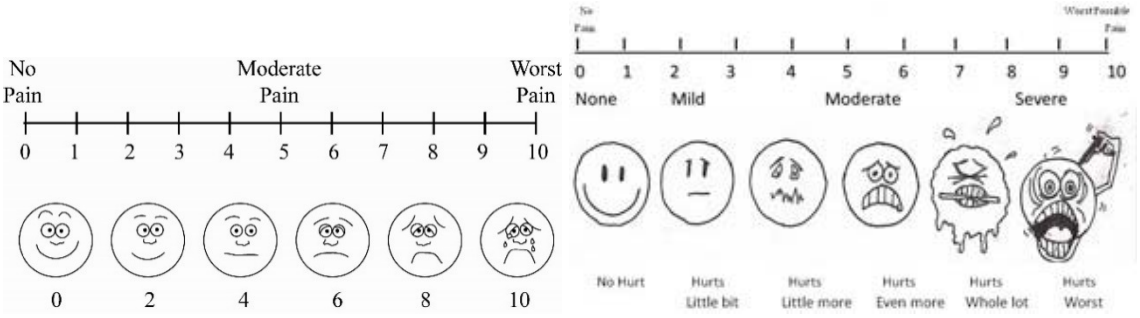
1.5.4.4 Hyperalgesic states following acute opioid exposure

In addition to chronic opioid exposure, OIH has also been reported following acute exposure. A number of studies have reported that the perioperative use of remifentanil is associated with hyperalgesia (e.g. Joly *et al.* 2005; Richebe, *et al.*, 2011; Song, *et al.*, 2011) and that this effect is dose-dependent (Fletcher and Martinez, 2014). Furthermore, the extent of postoperative wound hyperalgesia (i.e. the size of the area around the incision wound sensitised to mechanical pressure) has been shown to be strongly correlated with the risk of developing persistent pain following surgery (De Kock, *et al.*, 2001; De Kock, *et al.*, 2005; Lavand'homme P, 2005; Salegros *et al.* 2010). Taken together, these findings suggest that even acute opioid exposure can be associated with long-term challenges in effective pain management, via the mechanism of OIH. The principal issue in perioperative studies, however, is the almost exclusive use of remifentanil. The elevated incidence shown in these studies may be associated with the pharmacological properties of remifentanil, since it is an ultra-short-acting opioid. The abrupt offset of analgesia associated with cessation of remifentanil may result in over-identification of hyperalgesia.

1.5.4.5 Appropriated selection of pain assessment methods in the examination of opioid-induced hyperalgesia

The method of pain assessment is an important consideration when examining OIH. The two prominent methods are: patient reports (primarily visual analogue scales (VAS) or numeric rating scales (NRS)); and quantitative sensory testing (QST). There are a number of limitations

associated with the use of VAS/NRS. First, in order to distinguish between tolerance and hyperalgesia, it is wise to test experimental pain models at non-painful sites. The use of rating scales makes it difficult for patients to distinguish between persistently-experienced pain at one site and experimental pain at another site. Pain threshold and tolerance values assessed using QST create a focus on the target, non-painful site. Secondly, in the presence of persistent and debilitating pain, it may be difficult for some patients to understand that they are probably not experiencing the worst possible pain imaginable (i.e. a rating of '10'). Thirdly, in an extension of this argument, Berry (2012) proposed that the commonly-used Wong Baker-type rating scale, which employs the use of faces expressing emotion, may be unhelpful in assisting patients to understand the uppermost limit of rating scales. He suggested that the crying face does not convey 'worst imaginable pain' and that the faces need to be more expressive in helping patients to understand the meaning of these scales. The Wong Baker Scale and an example scale proposed by Berry are shown in ***Figure 1.1***.



Conventional Wong Baker Scale ***Example scale proposed by Berry (2012)***

Figure 1.1: *Representations of the Wong Baker Scale (left) and the scale proposed by Berry (right) for the assessment of pain.*

It is easy to imagine scoring pain differently on these two scales, since the uppermost face in the Wong Baker Scale is somewhat akin to the fourth face on Berry's proposed scale, and not at all representative of worst imaginable pain. A meta-analysis involving pain rating scales would necessarily need to be able to make the assumption that all 0-10 rating scales are comparable and understood in the same way by all patients; however, this is unlikely to be the case. Fourthly, the assessment of the psychometric properties of the Wong Baker and similar scales has primarily involved examining correlations between visual analogue scales and, occasionally, numeric rating scales. A more convincing assessment of the validity of such instruments would involve assessing the relationship between the scores reported and the findings generated by psychophysics techniques.

1.5.4.6 The need for further empirical evidence

Whilst the phenomenon of OIH is well-documented in preclinical models, as discussed, the translatability of these findings to clinical settings is questionable. Indeed, the findings of clinical studies have been comparatively less consistent. Given the predominance of case reports in this field of study, an initial step towards understanding the clinical relevance of this phenomenon may involve synthesis of currently-available empirical data from larger-scale studies. Whilst verification of OIH in humans may be only an initial step towards effective management of the condition, it may highlight issues for further consideration – such as, the need to characterise the extent of the problem by establishing prevalence in different clinical populations. The development of effective policy and practice relies on direction from robust evidence bases. This would not only include verification of the phenomenon in clinical settings and estimates of prevalence, but also examination of how treatment characteristics impact on the potentiation and attenuation of hyperalgesic states. This may include factors such as: treatment setting (ORT or analgesic treatment); duration of opioid exposure; therapeutic opioid dose; and the role of adjunctive treatments such as NMDA receptors antagonists.

1.5.5 Causal relationship between chronic pain and opioid abuse

Irrespective of a primary, or initial, diagnosis of chronic pain or opioid-related substance use disorder, patients with chronic pain in receipt of ORT are generally treated as an homogenous clinical population; however, this approach may deter effective management of these conditions. Chronic pain and opioid-related substance use disorder are commonly-occurring comorbidities for a number of reasons. First, substance use disorders can develop as a consequence of chronic pain via the mechanisms of iatrogenic addiction to opioids or pseudoaddiction. Secondly, opioid-dependent patients are shown to be associated with increased exposure to situations that result in physical trauma, violence and injury (NIDA, 2017) and, furthermore, pain may be more likely to develop in patients with opioid-related substance use disorders since pain intolerance has been well-documented in opioid-dependent patients. The literature suggests that OIH may exacerbate pain in opioid-dependent patients (e.g. Zahari *et al.*, 2016; Hay *et al.*, 2009; Compton *et al.*, 2001). Substance use disorders are chronic, relapsing conditions and ORT programmes are associated with relatively poor recovery rates with small numbers achieving long-term abstinence (Hser *et al.*, 2015). The delivery of effective treatment is dependent upon accurately profiling and responding to the clinical challenges associated with patients in ORT programmes and, as such, it would be short-sighted to assume patients to be an homogenous clinical population. Disease trajectories are perhaps one example of the issues that need to be considered in the development of effective treatment strategies. As such, there is a need to establish whether patients whose substance use disorder resulted

from chronic pain present with different clinical profiles and treatment requirements to patients whose chronic pain resulted from substance use disorders.

Iatrogenic dependence on opioids is a well-documented phenomenon with addiction reported in up to 8% of patients in receipt of opioid analgesic treatment (Volkow & McLellan, 2016). Whilst this figure represents a relatively low risk of addiction associated with opioid analgesic prescribing, these patients may constitute a substantial proportion in treatment for opioid dependence. Indeed, in an examination of patients being treated with ORT, Jamison and colleagues (2000) reported that 44% of those with chronic pain believed that prescribed opioid analgesics led to their addiction problems. In addition, the phenomenon of pseudoaddiction could account for further patients with chronic pain eventually being treated in ORT programmes. Pseudoaddiction is difficult to diagnose prospectively; this is usually only achieved on retrospectively observing a decrease or cessation of illicit substance use following the delivery of adequate analgesia. Lusher and colleagues (2006) reported that one of the strongest predictors of pseudoaddiction is disputes between patient and physician concerning analgesic use. Since disputes concerning treatment and opioid dose may be a common feature in ORT treatment settings, pseudoaddiction is unlikely to be effectively treated, and may even be potentiated, in these clinical settings. Conversely, pain development, exacerbation or prolongation can be a function of opioid dependence (e.g. Zahari, 2016) – via the phenomenon of OIH.

It is thus clear that a substantial proportion of patients in ORT programmes may have reached these clinical settings as a result of treatment or undertreatment for chronic pain and, furthermore, that patients entering ORT treatment facilities may have subsequently developed chronic pain problems following entry to ORT treatment. Whilst they may be treated as an homogenous comorbid clinical population within ORT treatment settings, the clinical presenting profiles and, therefore, the treatment requirements, may differ dependent upon the temporal or causal relationship and interaction between these two conditions. There are difficulties, however, associated with establishing, retrospectively, the primary, or initial, disorder occurring in comorbid patients. Simply examining which was diagnosed or treated first is likely to be biased. Whilst patients experiencing pain are likely to find the condition problematic following onset of symptoms, people with opioid-dependence may identify their condition as 'problematic' and, consequently, seek treatment at a relatively later stage in disease development. The patient-attributed direction of the causal relationship between chronic pain and opioid-related substance use disorder may provide a more reliable indication of the causal, or at least temporal, relationship between the two conditions.

1.6 Summary

Chronic conditions, particularly those associated with pain disorders, are becoming increasingly prevalent and burdensome on individuals and on society. Chronic pain is associated with relatively poor health and quality of life outcomes and also with relatively high service utilisation. In an effort to treat chronic and debilitating pain, physicians often must rely upon opioid analgesics. Whilst their analgesic efficacy in the long term is yet to be consistently demonstrated, there is no current alternative contender. Furthermore, whilst opioids are not demonstrated to be consistently effective in the long term, they remain unrivalled in the control of pain in the intermediate term. The increase in opioid prescribing has been suggested to be paralleled by an increase in opioid abuse. Iatrogenic addiction to opioids is well-documented and, even in the absence of a clinical diagnosis of opioid dependence, this may be a contributory factor in the development of opioid misuse. This should be a key concern for patients, practitioners and policy-makers and there is evidence to suggest that, without adequate information concerning risk of opioid dependence in individuals, physicians may be denying treatment to patients or to particular patient groups – with or without robust, empirical justification.

Physician trepidation over prescribing opioids to manage pain may have been fuelled by correlational data from the past two decades linking increased prescribing rates with increasing opioid dependence and abuse. This implied causal relationship has not yet been demonstrated, however, in large-scale empirical studies. Whilst a number of research teams have attempted to address this issue by undertaking systematic reviews and meta-analyses of data from available studies, the validity of their findings is questionable and the translatability of their findings is limited. The principal limitation in much of this work, to date, is the failure to control for pre-existing illicit and nonmedical opioid use. In examining the prevalence, rather than incidence, of problematic opioid use in patients exposed to opioid analgesic treatment, many of these studies are unable to suggest a causal relationship between analgesic prescribing and opioid abuse. A further complication in many of these reviews is the ambiguous use of terms – such as ‘abuse’, ‘misuse’, ‘addiction’, ‘dependence’, and so forth – and the inclusion of articles that use these terms in undefined ways. To ensure that patients are not unnecessarily denied adequate analgesic treatment, it is essential to synthesise high quality, robust empirical data examining *de novo* incidence of clearly-defined opioid dependence and abuse. An initial step in understanding the relationship between opioid prescribing and problematic use may be to consider examining the development of a clinically-diagnostic opioid use disorder.

Certain physiological factors, such as genetic predisposition and structure and function of the central nervous system, are proposed as risk factors for opioid abuse. Whilst genetic and environmental factors may be associated with the development of opioid abuse, these factors have not been specifically targeted in treatment settings to a significant extent since the appropriate depth and complexity of relevant information required would usually be unfeasible to determine during relatively short consultation sessions (Webster and Webster, 2005). A number of socioeconomic and individual characteristics have also been associated with the development and maintenance of opioid abuse and Ballantyne (2007) suggested that it is the presence of psychosocial, drug-related and physical factors that, together, indicate the risk of opioid abuse. The comorbid presentation of chronic pain and opioid dependence results in a clinically-complex challenge to physicians and policy-makers alike. Understanding the clinical challenges associated with the comorbid presentation of opioid-dependence and chronic pain is key to developing successful treatment strategies, which must aim to deliver effective pain management whilst minimising the risk of perpetuating or exacerbating problematic opioid use. Several studies have examined the clinical profiles or treatment outcomes in patients with comorbid chronic pain and opioid dependence – comparing them with either non-opioid-dependent patients with chronic pain or opioid-dependent patients with no pain – but no studies, to date, have attempted to produce a comprehensive profile of the clinical challenges, including treatment outcomes, associated with this comorbid patient group. The development of effective treatment strategies must be dependent upon identifying the clinical complexities of this comorbid patient population, and this must include a comprehensive understanding of mortality, additional morbidities, treatment characteristics and clinical outcomes.

The relationship between opioid dependence and chronic pain is dynamic and, in consequence, the cause-effect relationship between the two is not readily quantifiable. Whilst opioid-dependent patients with comorbid pain are, generally, considered to be a relatively homogenous group in ORT programmes, concerning the presence of pain, this may not be the case. Addicted populations are reported to misuse substances in an effort to experience either euphoria or a numbed emotional state. In contrast, pseudoaddiction is proposed to be a response to unmet analgesic requirements. The principal difference in pseudoaddiction, therefore, is that substance misuse should reduce or cease when analgesic requirements are met. Ilgen and colleagues (2010) examined the relative temporal onset of pain and substance use disorders and provided a general profile of each group. Whilst they identified the importance of understanding disease trajectories in developing appropriate treatment strategies for distinct clinical groups based on underlying problems, their study was not designed to provide comprehensive clinical profiles of these groups or to assess the effect of treatment

on outcomes. Relatively more extensive clinical group profiles are required in an effort to understand the treatment requirements associated with particular disease trajectories. Furthermore, identification of the underlying motivation for drug use is key to developing effective treatment strategies. As such, it is important to establish if there are clinically-distinct patient groups that reduce or cease problematic drug use following increasing analgesic doses or the introduction of adjunctive pain treatments.

Despite an underlying motive of control of unmanageable pain, increasing opioid doses may be unsuccessful in controlling pain and reducing illicit drug use in some patients. Increasing opioid doses may, instead, elicit an opioid-induced hyperalgesic state, which could result in increased pain sensitivity and exacerbation of the pain experience. This may result in continued or increased illicit drug use in efforts to control pain. Whilst the appropriate clinical response in this situation would be opioid rotation, reduction or cessation, this is rarely an option in opioid-dependent patients in receipt of ORT. The presence of OIH in treatment-seeking, opioid-dependent patients with chronic pain would, therefore, present complex clinical challenges. There is evidence to suggest that treatment with an NMDA receptor antagonist could reverse hyperalgesia through blocking glutamate-associated activation of these receptors. Evidence for OIH and the potentially therapeutic role of NMDA receptor antagonists has been well-documented in animal models; however, the evidence is relatively sparse and less consistent in clinical populations. There is evidence to suggest that, due to the cognitive components impacting on the experience of pain and the difficulties in definitively identifying pain in animals, it is questionable if pain assessment in preclinical models measures the same phenomenon as in clinical models. The presence of OIH in clinical populations could impact adversely on both pain management and control of problematic substance use, particularly in patients in receipt of ORT, and would present complex clinical challenges for both physicians and policy-makers. Given the small-scale nature of existing studies in clinical populations and the difficulties in identifying entirely satisfactory models for assessing hyperalgesia, synthesis of existing evidence may provide a valuable initial step towards informing policy, guiding the development of effective treatment strategies and highlighting directions for further research.

1.7 Objectives

Broadly speaking, the overarching aim of the present thesis was to explore the clinical implications of comorbid chronic pain and opioid dependence disorders. This aim was addressed using a multimethod approach to examining the available data. A health informatics approach was used to facilitate primary data analyses on routinely-available clinical data with the aim of addressing two broad questions:

(1) What are the clinical characteristics and treatment outcomes associated with comorbid chronic pain in treatment-seeking, opioid-dependent patients?

(2) Is the patient-attributed direction of the causal relationship in the development of chronic pain and opioid dependence associated with the identification of two clinically-distinct groups with differing treatment requirements?

Systematic review and meta-analytical approaches were used to facilitate secondary data analyses addressing two questions:

(3) What is the incidence of iatrogenic clinically-diagnostic opioid dependence or abuse following opioid analgesic treatment?

(4) Is there evidence of opioid-induced hyperalgesia in humans?

1.8 Terminology

The terms 'dependence' and 'abuse' are used in the present thesis to indicate a clinically-diagnostic disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The term 'misuse' is used to indicate illicit or nonmedical substance use, irrespective of whether or not clinically-diagnostic criteria are met. The term 'tolerance' refers to a state whereby increasing analgesic doses are required to obtain the original therapeutic effect.

Chapter 2

Methods used in primary data analysis

A multimethod approach was used in the present thesis; both primary and secondary data analyses were undertaken in addressing the thesis objectives. The findings of the two systematic reviews (chapters 5 and 6) are reported in accordance with the recommendations set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). In consequence, the methods used in these reviews are reported in their respective chapters. The present chapter details the methods used in the primary data analysis.

2.1 Participants and setting

Participants were drawn from the NHS Tayside Substance Misuse Service (TSMS). This clinical facility is divided into two treatment streams: the Tayside Alcohol Problem Service (TAPS); and the Tayside Drug Problem Service (TDPS). Participants were drawn exclusively from the latter treatment stream. All patients entering TDPS are dependent upon opioids, primarily heroin, on entry to treatment, and many also engage in poly substance misuse. TDPS delivers opioid replacement therapy (ORT), exclusively in the form of methadone maintenance therapy (MMT). Opioid dependence is established in the service through tests of tolerance and withdrawal, which are used to inform the commencement dose of methadone. Testing continues throughout the titration phase until patients are stabilised on optimum doses.

A battery of assessments was completed for the entire treatment population (n=626) in 2005, in response to a TSMS decision to undertake a comprehensive clinical service review. Assessments were completed at routine clinical appointments by trained medical staff during 2005 and, on completion of the service review, all data were made available for research purposes. Whilst the aim was to complete all assessment instruments with all patients being treated in the service during that year (referred to as 'study inception'), a full battery of tests was not completed for all participants. Of the 626 patients in treatment, 521 (83%) completed a Brief Pain Inventory – Short Form (BPI-SF) in its entirety, the criterion for inclusion in the present study. The majority of those that were excluded (n=105) did not complete a BPI-SF, whilst a considerably smaller proportion did not complete the BPI-SF in its entirety. Duration of pain at study inception was required to identify chronic pain; therefore, where this was not

indicated on the BPI-SF, these patients were excluded from the present study. It is anticipated that those that did not complete a BPI-SF represented a group with no pain problems. Whilst staff were instructed to complete all study inception measures with all patients, it is common practice within the service to refrain from completing an instrument where no relevant problems exist. An additional possibility, however, is that some patients missed several routine clinical appointments and staff were unable to complete the full battery of tests alongside the demands of treatment delivery. So, whilst it might be assumed that the absence of a BPI-SF is indicative of no pain problems, in the absence of definitive evidence, these patients were excluded from the present study. In conclusion, the entire study cohort comprised 521 participants.

2.2 Materials

An extensive range of standardised instruments was used to collect data at study inception and routinely-available, nationally-held health registers provided data covering the follow-up period.

2.2.1 Data collected at study inception

A number of instruments were used to collect data across a range of domains at study inception: pain assessment; sociodemographic characteristics; addiction-related characteristics; and health and morbidity.

2.2.1.1 Brief Pain Inventory-Short Form (BPI-SF)

A modified version of the Brief Pain Inventory-Short Form (BPI-SF; Cleeland & Ryan, 1994) was used to identify pain at study inception and to profile pain-related characteristics in the study cohort. The BPI-SF is a 9-item questionnaire intended to assess the sensory and reactive dimensions of pain. Patients are asked to: rate their worst, least, average, and current pain intensity; list current treatments and their perceived effectiveness; and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life. Two subscale scores can be computed, one focusing on pain severity and the other on pain interference. The BPI-SF was modified in two ways, however, to meet the needs of the treatment service. First, the four 0-10 pain intensity scales were replaced with a single 0-100 scale. Secondly, some items were omitted from the instrument and, in consequence, computation of the pain severity and pain interference subscales was not possible. Data from individual items were used to identify duration, intensity and locus of pain, to characterise pain interference on sleep and daily activities, and to profile treatment for pain problems. The BPI-SF has been validated in a number of clinical populations, including patients

in receipt of methadone maintenance therapy for the treatment of opioid dependence (Dennis *et al.*, 2016).

2.2.1.2 Sociodemographic questionnaire

Sociodemographic data were collected at study inception using a proforma developed by the TSMS. Data were collected using an interview format and the proforma recorded: age; gender; 3 accommodation-related questions; 7 questions concerning dependent children; 12 health-related questions; 3 education-related questions; and 2 questions concerning support from other agencies.

2.2.1.3 Addiction-related data

A range of instruments designed for use with addicted populations was used to collect data at study inception. These instruments included information concerning illicit substance use, drug-related harm, general health and patient perceptions of ORT treatment.

2.2.1.3.1 Maudsley Addiction Profile (MAP)

The Maudsley Addiction Profile (MAP; Marsden *et al.*, 1998) was completed by participants at study inception. The MAP is a 60-question, clinician-administered instrument designed for research purposes and used in investigations of populations with drug and/or alcohol problems. It addresses four domains: (1) Substance use (quantity and frequency of use); (2) Health risk behaviour (injecting and sharing injecting equipment); (3) Health symptoms (physical and psychological); and (4) Personal/social functioning (relationships, employment and crime). Physical and mental health subscale scores can be calculated by summing scores for each of the 10 individual items on each of the subscales, resulting in a range of 0-40 for each subscale. Reliability and validity in substance misusers has been demonstrated for the MAP (Marsden *et al.*, 1998) and the MAP subscales (Marsden *et al.*, 1998; Sharma *et al.*, 1999).

2.2.1.3.2 Injecting Risk Questionnaire – Long Form (IRQ-LF)

The Injecting Risk Questionnaire – Long Form (IRQ-LF; Stimson *et al.*, 1998) was designed to profile sharing of injecting equipment, both 'direct sharing' (needles and syringes) and 'indirect sharing' (other injecting-related apparel such as spoons or filters). The IRQ is a 17-item questionnaire and the client self-report, agency setting (IRQ-SQ-A) version was used in this study. The first 16 questions are rated on a 4-point scale (never=0; rarely=1; sometimes=2; and frequently=3) with the total representing the injecting risk score; higher scores represent greater risk, with a maximum possible score of 48. The final question asks about the number of

people with whom clients have shared any injecting equipment in the preceding 4 weeks. The IRQ is shown to be reliable and valid in currently-injecting drug users (Stimson *et al.*, 1998).

2.2.1.3.3 Hyperhidrosis questionnaire

The hyperhidrosis questionnaire used in this study was developed by the TSMS. It is a 10-item instrument which comprises some of the core items from the standardised Hyperhidrosis Impact Questionnaire (HHIQ; Teale *et al.*, 2002) and one question focussing on the perceived role of ORT (specifically in this methadone-maintained population). Scoring of individual items is based on HHIQ scoring and all items are scored individually. The psychometric properties of the instrument have not been assessed.

2.2.1.3.4 Treatment Perceptions Questionnaire (TPQ)

The Treatment Perceptions Questionnaire (TPQ; Marsden *et al.*, 2000) was completed by participants at study inception. It is a self-report, 10-item brief scale designed to measure patient satisfaction with ORT treatment. It was developed at the National Addiction Centre in London and focusses on perceptions of:

1) Nature and extent of contact with a treatment programme's staff team (5 items)
2) Aspects of the operation of the treatment service and its rules and regulations (5 items)

Each item takes the form of a belief statement and patient response is recorded using a 5-point Likert-type scale ('strongly agree' to 'strongly disagree'). Item responses are weighted 0-4 (with a total score range of 0 to 40), and higher scores represent greater treatment satisfaction. Participants were asked an additional 4 questions concerning treatment perceptions; however, responses to these questions were not included in the total standardised score. The additional 4 questions addressed: difficulties with travel arrangements; treatment flexibility; regular feedback on progress; and clinic atmosphere. The reliability and validity of the TPQ has been demonstrated in patients in ORT programmes (Marsden *et al.*, 2000).

2.2.1.4 Psychiatric morbidity

Several standardised instruments were used to assess psychiatric morbidity at study inception. These instruments were used to indicate the presence of any psychiatric morbidity and the presence of specific psychiatric morbidities.

2.2.1.4.1 General Health Questionnaire (GHQ-28)

The 28-item version of the General Health Questionnaire (GHQ-28; Goldberg, 1978) was completed by participants at study inception. The GHQ-28 was designed as a screening tool to

indicate psychiatric diagnostic status. This self-report questionnaire comprises 28 questions on a 4-point scale ('*Not at all'*; '*No more than usual'*; '*Rather more than usual'*; and '*Much more than usual'*). Individual questions on the GHQ-28 can be scored using ether the GHQ method (0 to 3) or the Likert method (0,0,1,1) and 'caseness' thresholds are reported as 23/24 and 4/5, respectively. This study employed the used of the GHQ scoring method and applied the 23/24 threshold in identification of psychiatric 'caseness'. Through factor analysis, four subscales have been identified:

- Somatic symptoms (items 1-7)
- Anxiety/insomnia (items 8-14)
- Social dysfunction (items 15-21)
- Severe depression (items 22-28)

The GHQ-28 correlates well with the Hospital Depression and Anxiety Scale (HADS; Sakakibara *et al.*, 2009) and other standardised measures of depression (Robinson and Price, 1982). It has been shown to have the ability to accurately detect diagnoses in accordance with the Composite International Diagnostic Interview (CIDI; Goldberg et al., 1997). The reliability and validity of the GHQ-28 is well-documented in numerous clinical populations (e.g. Goldberg et al., 1997; Wernecke *et al.*, 2000; Robinson and Price, 1982; Sakakibara *et al.*, 2009; Failde and Ramos, 2000). Whilst acceptable levels of reliability and validity have been demonstrated for the GHQ-60 in substance misusers (Ross and Glasser, 1989), the psychometric properties of the GHQ-28 have not yet been assessed in this clinical population.

2.2.1.4.2 Clinical Outcomes in Routine Evaluation (CORE)

The Clinical Outcomes in Routine Evaluation – Outcome Measure (CORE-OM; Evans *et al.*, 2000) was completed by participants at study inception. It assesses the level of current psychological global distress and is designed to be administered before and after therapy, with comparison of pre- and post-treatment scores providing a measure of 'outcome'. A single point assessment, however, can provide group-level cross-sectional data about clinical status which can enable subgroup profiling and comparisons. The CORE-OM is a self-report questionnaire which can be supplemented by two clinician-reported instruments. The client-report questionnaire comprises 34 questions, each rated on a 5-point scale, concerning wellbeing during the preceding week. The total score (ranging from 0-136) can be divided by the number of questions (34, if all completed) to provide a total mean score for each participant (ranging from 0-4). Barkham e*t al.* (2006) subsequently established a means of interpreting the CORE-OM. Within their framework, total scores place participants into one of six categories of psychological distress ranging from 'healthy' to 'severe'. The first two categories are associated with non-

clinical status, and a total score of 34 or more confers clinical status. Total and mean scores can also be calculated for the following four dimensions:

- Subjective well-being (4 items)
- Problems/symptoms (12 items)
- Life functioning (12 items)
- Risk/harm (6 items)

Measures are problem-scored – i.e. higher scores indicate more problems. Interpretation of the 'subjective wellbeing' and 'life functioning' dimension scores are, therefore, counter-intuitive, with higher scores indicating poorer wellbeing/function; however, this enables consistent scoring across dimensions and the calculation of a meaningful total and mean scores. The range of the subjective wellbeing total score is 0-16; the range of the problems/symptoms and life functioning total scores is 0-48; and the range of the risk/harm total score is 0-24. Mean scores can also be calculated (by dividing the total score by the number of questions answered), ranging from 0 to 4. The CORE-OM is a non-proprietary measure of psychological distress and, since its development, it has been validated with samples from the general population and from NHS primary and secondary care settings (e.g. Evans et al., 2000; Barkham et al., 2001; Evans et al., 2002; Mellor-Clark and Barkham, 2000; Mellor-Clark and Barkham, 2006). Its validity is yet to be assessed in opioid-dependent populations.

2.2.1.4.3 Social Phobia Diagnostic Questionnaire (SPDQ)

The Social Phobia Diagnostic Questionnaire (SPDQ; Newman *et al.*, 2003) was completed by participants at study inception. It is a 16-item questionnaire that was designed as a diagnostic screening tool, used to assess social phobia in accordance with DSM-IV criteria. The instrument comprises several questions requiring 'yes' or 'no' responses and several symptom rating scales (5-point Likert scales scoring 0 to 4). Newman and colleagues proposed a summed total score system (range 0 to 27) with the aim of identifying a threshold score that would best enable detection of social phobia. Using ROC analysis, they identified that the optimal balance between sensitivity and specificity (both over 80%) was achieved using a diagnostic threshold of 7.38.

The validity and reliability of the SPDQ has been demonstrated in three studies involving undergraduate students (Newman *et al.*, 2003) but its psychometric properties are yet to be investigated in opioid-dependent populations. The SPDQ questions are designed to address two specific domains (fear and avoidance); however, the psychometric properties of these summary scores has not yet been investigated.

2.2.1.4.4 Impact of Events Scale (IES)

The Impact of Events Scale (IES; Horowitz *et al.*, 1979) was completed by participants at study inception. The IES provides a measure of the amount of distress associated with a specific event, and is the measure of posttraumatic stress disorder (PTSD) recommended by the NHS *Improving Access to Psychological Therapies* (IAPT) programme in England. It is a 15-item self-report questionnaire with two subscales: intrusion (items 1, 4, 5, 6, 10, 11, 14); and avoidance (items 2, 3, 7, 8, 9, 12, 13, 15). Item responses are recorded on a 4-point scale and weighted thus: 'not at all'=0; 'rarely'=1; 'sometimes'=3; and 'often'=5. Total scores range from 0 to 75. Threshold scores are not widely agreed upon and the current study used the total score thresholds identified by Hutchins and Devilly (2005):

0 – 8:	No meaningful impact
9 – 25:	Impact event – may be affected
26 – 43:	Powerful impact event – certainly affected
44 – 75:	Severe impact event – capable of altering functional ability

Scores of 26 and above are considered to be clinically important and are sometimes taken to be potentially indicative of PTSD. Coffey and Berglind (2006) suggest that a score of 27 or more is associated with a 75% chance of having PTSD, and Neal and colleagues (1994) suggest that scores of 35 and above represent the optimum threshold for a probable diagnosis of PTSD. Employing the use of a conservative approach, the latter proposed threshold (total score ≥35) was used in the current study as indicative of diagnostic status. The range of the intrusion subscale score is 0-35 and the range of the avoidance subscale scores is 0-40. The validity and reliability have been demonstrated and the IES has been shown to have high sensitivity in discriminating between patient and non-patient samples (Zilberg *et al.*, 1982; Joseph, 2000; Sundin and Horowitz, 2002).

2.2.2 Data collected during the follow-up period

Data pertaining to health and medical treatment were obtained for the follow-up period. Clinical data were collected directly from participants using one standardised instrument, and relevant routine health data extracts, spanning the observation period, were provided by a national Safe Haven. The Health Informatics Centre (HIC) Services Safe Haven was selected as a repository for accessing, hosting and linking electronic datasets. HIC Services is a University of Dundee research support facility which is situated within the Farr Institute @ Dundee and run in collaboration with NHS Tayside and NHS Fife. HIC Services operates one of the secure national Safe Havens and is government-certified as a Trusted Third Party (TTP). This Safe Haven was in receipt of regular data feeds from routinely-available, nationally-held clinical registers.

2.2.2.1. Treatment Outcome Profile (TOP)

The Treatment Outcome Profile (TOP; Marsden *et al.*, 2008) was developed as part of the National Drug Treatment Monitoring System (NDTMS) in England and forms part of the NDTMS core dataset. It is a clinical-rated instrument comprising 20 questions, focussing on: substance use; injecting risk; criminal behaviour; health; and quality of life. Questions that overlap with the MAP are formatted identically enabling clinical data for individuals to be investigated over time, irrespective of which instrument was used. The TOP was completed at regular intervals during the follow-up period and was used to provide follow-up data to the MAP. Reliability and validity of the TOP was demonstrated in clinical populations in receipt of ORT (Marsden *et al.*, 2008).

2.2.2.2 Death Certification

An extract of the Death Certification Register was provided by HIC Services. This included information pertaining to date and cause of death.

2.2.2.3 Biochemical laboratory data

An extract of the NHS Tayside biochemical laboratory dataset was provided by HIC Service. This dataset included the results of all drug screens undertaken by the TSMS. This dataset was used to identify all positive and negative results for opioids, benzodiazepines and cannabinoids.

2.2.2.4 Community-dispensed prescribing

An extract of the Prescribing Information System (PIS) dataset was provided by HIC Services. This dataset includes all information concerning community-dispensed prescribing, organised by disease intended to treat, in accordance with the International Classification of Diseases (ICD) coding system.

2.2.2.5 General hospital admissions

An extract of the Scottish Morbidity Record, General / Acute Inpatient and Day Case (SMR01), was provided by HIC Services. This register includes information on length of stay and diagnosis on discharge for all patients admitted to general hospital inpatient or day case facilities. Diagnostic codes are assigned in accordance with the ICD.

2.2.2.6 Psychiatric hospital admissions

An extract of the Scottish Morbidity Record, Mental Health Inpatient and Day Case (SMR04), was provided by HIC Services. This register includes information on length of stay and diagnosis on discharge for all patients admitted to psychiatric hospital inpatient or day case facilities. Diagnostic codes are assigned in accordance with the ICD.

2.3 Procedure

Data were collected for all participants at study inception (throughout the calendar year 2005), and during the 5-year follow-up period.

2.3.1 Data collection at study inception

The full battery of tests was completed at routine clinic appointments with specialist addiction nurses. Staff were trained on administration of these instruments, to ensure uniformity in data collection procedures. The order in which data were to be collected was pre-specified, again, to ensure uniformity. Staff were instructed to complete all instruments with all patients, irrespective of whether or not they were experiencing relevant problems. For example, if an individual had no pain problems, staff were still required to administer a BPI-SF, indicating that there were no pain problems. An electronic extract of each of the HIC-hosted registers was also provided for the study inception year (2005).

2.3.2 Data collection during the follow-up period

An electronic extract of each of the HIC-hosted registers was provided for each year of the follow-up period, in addition to the study inception year. Whilst data concerning the biochemical drug screens were obtained from a nationally-held register, these data were dependent upon urine samples having been obtained in the clinic setting. The NHS TSMS treatment service aims to complete TOPs and undertake drug screens, by urinalysis, every three months with each patient. The amount of missing data indicates that this was not achieved for all patients. It is unclear whether this was due to missed appointments or for some other reason. Given the extent of missing data, however, this is unlikely to be solely a function of missed appointments. Whilst the aim was to select TOP data at 5-year follow-up, exactly, in light of the extent of missing data, the TOP nearest the target date in 2010 was selected. Where no TOP data were available from 2010, a null value was returned and participants were excluded from follow-up analyses involving data from the TOP. As described below (section 2.3.5.1), drug screen data from the entire 2010 calendar year were used in assessing illicit drug use at follow-up.

2.3.3 Electronic data hosting and linkage

The NHS Community Health Index (CHI) number, a 10-digit unique NHS patient number, is used as the principal identifier for linking and then anonymising datasets prior to release to research teams. In the present study, all data collected in the clinic setting, along with a list of appropriate CHI numbers, was uploaded to the HIC Services Safe Haven. The CHI numbers were used, by HIC Services, to extract relevant data from national registers. A proxy CHI ('proCHI') identifier was assigned to all data to facilitate linkage across datasets. Statistical analyses of primary data were, therefore, undertaken within the secure virtual environment provided by HIC Services.

2.3.4 Identification of target groups within the study

A case-control design was employed in this study; the target group comprised treatment-seeking, opioid-dependent patients with comorbid chronic pain and the control group comprised treatment-seeking, opioid-dependent patients with no pain.

2.3.4.1 Identification of chronic pain

Duration of pain at study inception was assessed using the BPI-SF. Three temporal thresholds have been establish to identify chronic pain: 3 months; 6 months; and 12 months (Smith *et al.*, 2008). In the present study the chronicity threshold was set at 12 months, which is used less frequently than the 3- and 6-month thresholds. The rationale for employing the use of the 12-month threshold was that, in a clinical population familiar with persistent, debilitating conditions, the highest of the three established thresholds would be most appropriate.

2.3.4.2 Identification of patient-attributed direction of the causal relationship between chronic pain and opioid dependence

The patient-attributed direction of the causal relationship between chronic pain and opioid dependence was ascertained by direct questioning. Patients were asked were, 'Do you think that your pain problems caused addiction or that addiction caused your pain problems, or do you think that they are unrelated?' Participants who indicated that the two were unrelated were excluded from this part of the study.

2.4 Data preparation

Many of the data items used in the present study were presented in the form of alpha-numeric characters. Coding of these data items was, generally, uncomplicated; however, there was a need to compute several new variables from the original data. This section details the method

used for the identification of illicit drug use, and the methods used to enable comparison of opioid and sedative medication doses.

2.4.1 Identification of illicit drug use

As discussed previously, urinalysis is associated with a relatively high risk of false-positive and false-negative results. In consequence, a more robust means of detecting illicit drug use was devised. As part of the standard TSMS service requirement, staff are directed to obtain urine samples from patients at least every three months; however, some patients undergo more or less drug testing than is directed. Illicit drug use was concluded where there were at least three positive test results in that year.

2.4.2 Equianalgesic computations

Morphine-equivalent doses were established using an online equianalgesic calculator based on the American Pain Society guidelines and critical review papers focusing on the issue of equianalgesic dosing (http://clincalc.com/opioids/). The website highlights that, due to interpatient variability, clinical judgement should be used in conjunction with the calculator; however, for research purposes, consistent conversion methods are of key importance. This calculator was selected for two principal reasons. First, reliability: the extensive number of conversion algorithms available means that most opioid prescriptions in the datasets can be converted using one calculator and consistent conversion methods. Secondly, validity: the extensive research undertaken in developing the conversion algorithms is likely to result in valid conversion ratios – relatively so, considering the acknowledged interpatient variability. The morphine-equivalent dose for each of the opioid medications from the present study is reported in ***Table 2.1***. The conversion ratios associated with methadone are dose-dependent and are shown separately in ***Table 2.2***. Buprenorphine was not available for conversion in the equianalgesic calculator so the Monthly Index of Medical Specialities (MIMS) conversion ratio (x80) was applied. Only one formulation and strength of buprenorphine was used to provide analgesia (200mcg tablets) which equated to a 16mg oral morphine-equivalent dose. It is acknowledged that the morphine-equivalents of tramadol and methadone have not been reliably established (Mercadante *et al.*, 2011); whilst the conversion ratios vary substantially for each of these drugs using different equianalgesic calculators, in an effort to maintain consistency, the same calculator was used for all possible conversions (i.e. for all drugs excepting buprenorphine). In the case of methadone conversion ratios, there was a considerable overlap in oral methadone doses. The present study used the mid-point of the overlap as the threshold value for each conversion ratio. The thresholds used in the present study are also reported in ***Table 2.2***.

Table 2.1: *Morphine-equivalent dose for opioid medications in the present study*

Approved name	Formulation	Strength	Measure	Oral morphine equivalent dose
Buprenorphine	Tablets	200	mcg	16
Codeine phosphate	Tablets	15	mg	2.1
Dihydrocodeine tartrate	Tablets	30	mg	3
Fentanyl	Patch	12	mcg/hr	72
Fentanyl	Patch	50	mcg/hr	300
Meptazinol	Tablets	200	mg	6
Morphine	Capsules	60	mg	60
Morphine	Solution	10	mg/5ml	10
Morphine	Tablets	5	mg	5
Oxycodone	Tablets	20	mg	20
Tramadol hydrochloride	Capsules	100	mg	10
Tramadol hydrochloride	Tablets	100	mg	10

Table 2.2: *Dose-dependent morphine-equivalent ratios for methadone*

Direct methadone-morphine conversion		
24 hour oral methadone total dose (recommended range)	Threshold dose used in present study	Conversion ratio (oral methadone to oral morphine)
< 15 mg	<12 mg	1:2
8-25 mg	12-19 mg	1:4
13-37 mg	20-31 mg	1:8
25-42 mg	32-37 mg	1:12
33-67 mg	38-58 mg	1:15
> 50 mg	>58 mg	1:20

2.4.3 Equisedative computations

Benzodiazepines are the most commonly prescribed anxiolytic and, in the current study, all but one of the prescribed anxiolytics were benzodiazepines: diazepam (10,552 prescriptions); chlordiazepoxide (23 prescriptions); lorazepam (33 prescriptions); and oxazepam (1 prescription). Since 98% of all benzodiazepine prescriptions consisted of diazepam, for comparison, all other benzodiazepine doses were converted to diazepam-equivalent doses. Whilst morphine-equivalent doses are the standard for comparing opioid doses, there are a number of differences which make it difficult to establish accurate conversion ratios between

benzodiazepines. These include: potency; speed at which they are metabolised and eliminated; rate of accumulation; and degree of sedation. In consequence, a wide range of conversion ratios are documented. ***Table 2.3*** reviews common conversion ratios and indicates the conversion ratio selected for use in the present study. Ratios were selected based on mode average.

In total, 97 buspirone hydrochloride prescriptions were dispensed to 10 cases during the observation period (0.9% of all dispensed anxiolytic prescriptions). Buspirone hydrochloride is a non-benzodiazepine anxiolytic and the mechanism of action of this drug is not well-understood. Clinically, it differs from typical benzodiazepine anxiolytics in that it does not exert anticonvulsant or muscle relaxant effects and it lacks the prominent sedative effect associated with more typical anxiolytics. From a pharmacological perspective, unlike typical benzodiazepines, buspirone is reported to have a high affinity for serotonin (5-HT1A) receptors and no significant affinity for benzodiazepine receptors; furthermore, it does not affect gamma-Aminobutyric acid (GABA) binding *in vitro* or *in vivo* when examined in preclinical models. It would not be feasible to attempt to establish a diazepam-equivalent conversion ratio and, since the total number of buspirone prescriptions dispensed accounts for a very small proportion of the total number of dispensed anxiolytic prescriptions (0.9%), buspirone was excluded from calculations involving anxiolytic doses.

Table 2.3: *Common diazepam-equivalent conversion ratios and selection of the ratios for use in the present study.*

	Diazepam	**Chlordiazepoxide**	**Lorazepam**	**Oxazepam**
BNF (2012)	5mg	15mg	0.5-1mg	15mg
Taylor *et al.* (2012)	5mg	12.5mg	0.5mg	15mg
Bazire (2012)[a]	5mg	15mg (10-25mg)	0.5-1mg at 4mg/d 2mg at 5mg/d	15mg (10-40mg)
DoH (2007)	5mg	15mg	0.5mg	15mg
Ashton (2002)[b]	5mg	12.5mg	0.5mg	10mg
ClinCalc (2016)	5mg	25mg (6-25mg)	1mg (0.25-2mg)	10mg (2.5-20mg)
Present study	***5mg***	***15mg***	***0.5mg***	***15mg***

2.5 Statistical considerations

Data were analysed, using the Statistics Package for Social Scientists (SPSS) v.22, within the HIC Services Safe Haven virtual environment. This section provides an overview of the statistical tests used in the data analysis, and addresses relevant issues associated with testing.

2.5.1 Univariate analysis of categorical dependent variables

The chi square test was used in the analysis of categorical dependent variables by categorical independent variables. As is the case with many statistical tests, the chi square generates p-values that are approximations, which only become exact when sample sizes reach infinity. As such, analysis of large samples generates relatively accurate p-values; however, p-values are likely to be too conservative in the analysis of smaller samples. The Fisher's exact test was considered for analysis of the data, but it is also associated with limitations. After consideration, it was decided that the samples in the present study were sufficiently-sized to employ the use of the chi square test.

Since multiple comparisons can result in Type I errors (i.e. false positive results), the familywise error rate was controlled, using a manual Bonferroni correction, where one hypothesis was addressed using multiple testing. The familywise error rate (set at the conventional 0.05) was divided by the number of tests associated with one single hypothesis to establish the critical value (α) for individual tests. Where the critical value was adjusted, this was recorded in the text or table footnotes.

Statistical findings were reported as chi-square value and degrees of freedom ($\chi^2(df)$), probability value (p) and effect size, Pearson's Phi or Cramer's V (ω). Pearson's Phi was used to assess the effect size in 2x2 contingency tables and Cramer's V was used where there were more than two levels in independent variables. Descriptive summary data were presented as number of event (n) and percentage of group (%).

2.5.2 Univariate analysis of continuous dependent variables

Univariate analysis of variance (ANOVA) was used to assess continuous dependent variables by categorical independent variables. The first, and most important, assumption of the univariate ANOVA is independence of cases. The only occasion on which this assumption was violated was during repeated measures analyses, and a repeated measures ANOVA was used in these circumstances.

The second assumption of the univariate ANOVA is that the data are normally distributed. The F statistic is considered to be robust to slight violations of the assumption of normality. Furthermore, it is robust to skewed or kurtotic distributions, but platykurtosis (a substantially flatter distribution than the Gaussian curve) can have a profound effect on the Type I error rate when sample sizes are small, resulting in the generation of false positive results. Whilst sample sizes were not particularly small, skewness and kurtosis were investigated in addition to normality. In the event that the distribution assumptions were seriously violated, the non-parametric Kruskal-Wallis H test would have been used in place of the univariate ANOVA; however, this was not required. Extreme outliers were excluded from analyses, as per convention, to prevent distortion of results.

The final assumption of the univariate ANOVA is homogeneity of variance. The F statistic is not particularly robust to violations of this assumption. Since this study design generated a balanced model, with relatively equal numbers in groups, if the ratio of the largest variance to the smallest variance was 4 or less, the F test was considered to be valid. Levene's test was used to assess homogeneity of variance and, if this assumption had been violated, Welch's ANOVA would have been used, since it is generally considered to be superior to the Brown and Forsythe test. There was, however, no requirement for non-parametric testing.

In conclusion, there were no serious violations of the parametric assumptions; therefore, the univariate ANOVA was used to analyse group differences in continuous dependent variables. Where there was a risk of Type I errors occurring, due to multiple comparisons, a Bonferroni correction was applied to the univariate ANOVA; therefore, the familywise error rate was not adjusted and the critical value remained at $\alpha = 0.05$.

Statistical findings of the univariate ANOVA were reported as F value, between-subjects degrees of freedom and within-subjects degrees of freedom (F(between-subjects df, within-subjects df)), probability value (p) and effect size, partial eta squared (η_p^2). Descriptive summary data were presented as mean value ($\bar{x}$) and standard deviation around the mean (σ).

2.5.3 Repeated measures analysis of continuous dependent variables and adjustment for multiple comparisons

Repeated measures ANOVA was used to analyse continuous within-subjects factors that were measured at more than one point in time. Sphericity is an important assumption of the repeated-measures ANOVA. Sphericity is present where the variances of the differences

between all possible pairs of independent variable levels are equal, and violations of sphericity occur where the variances of the differences are not equal. As such, sphericity can be likened to homogeneity of variances in a between-subjects ANOVA (discussed above). Violations increase the risk of Type I errors, resulting in false positive findings. The Mauchley Sphericity Test was used to identify violations of sphericity and, where present, to identify the appropriate method of adjustment in order to produce a more valid critical F-value and, thereby, reduce the Type I error rate. Where sphericity was violated, indicated by a significant p-value on the Mauchley Sphericity Test, and the measure of sphericity, epsilon (ε), was less than 0.75, a Greenhouse-Geisser correction was applied. Where epsilon was 0.75 or greater, a Huynh-Feidt correction was applied. A Bonferroni correction was applied in the repeated measures ANOVA procedure to compensate for multiple comparisons; therefore, the familywise error rate was not adjusted and the critical value remained at $\alpha = 0.05$. The repeated measures ANOVA generates the same statistics and descriptive summary data as the univariate ANOVA.

2.5.3.1 Repeated measures analysis of mean and maximum morphine-equivalent opioid dose and diazepam-equivalent anxiolytic dose

The mean dose of medication was calculated in person-years – i.e. the mean dose was calculated for each patient for each year and the mean average of the individuals' mean values was reported. To facilitate repeated measures of the mean and maximum doses of opioids and benzodiazepines with a meaningful number of participants, rather than simply the very small proportion that was in receipt of these medications during the entire observation period, those that had received prescriptions for that medication at any point during the observation period were included and were assigned a value of 0mg for years during which they received no prescriptions. Whilst these analyses permitted exploration of the overall effects of group and time and interaction effects, absolute mean dose was 'diluted' since all individuals that were in receipt of that particular medication at any point during the observation were included (but were assigned 0mg for each year that no prescriptions were received). In order to establish an accurate mean dose for each year, and to enable group comparisons based on the 'absolute' mean dose, univariate analysis of variance was undertaken for each year. In each case, these findings are shown beneath the findings of repeated measures analyses.

2.5.3.2 Repeated measures analysis of number of prescriptions

Many participants were treated with prescribed medications intermittently during the observation period and, in consequence, the absence of treatment for one or more years often did not indicate complete cessation of treatment. To facilitate repeated measures of the number of prescriptions with a meaningful number of participants, rather than simply the very

small proportion that was in receipt of particular medication during the entire observation period, the method described above was employed. Those that had received prescriptions for that medication at any point during the observation period were included and coded with a zero for years during which they received no prescriptions.

2.5.4 Univariate prediction of binary target variables

Binary logistic regression was used to assess the independent predictive capacity of categorical and continuous predictor variables on binary target variables. The assumptions of binary logistic regression are not particularly restrictive. First, the outcome variable must be binary, and comprised of mutually exclusive and exhaustive categories. Secondly, predictor variables must be either continuous or binary; if categorical variables with more than two levels are included, dummy variables must be created. In the present study, all predictor variables were either continuous or binary. Tables show the number of participants in each analysis (n), odds ratio (OR), 95% confidence interval (95% CI) and probability value (*p*).

2.6 Required permissions

Guidance was sought from the East of Scotland Research Ethics Committee (EoSREC). It was determined that ethics approval was not required, due to the data being fully anonymised prior to release for data analysis. HIC Services works with full EoSREC ethics approval but this is not required for individual 'HIC-badged' studies. All work involving NHS data was undertaken with the agreement of the NHS Tayside Caldicott Guardian and the NHS Tayside Research and Development (R&D) Department.

Chapter 3

Comparison of patients with and without chronic pain in a clinical population in receipt of opioid replacement therapy (ORT) for the treatment of opioid dependence, and evaluation of key ORT treatment outcomes in these two groups

3.1 Introduction

The ineffective management of any medical condition necessarily confers considerable personal, societal and economic burdens; however, amplified personal, social and financial costs may be associated with specific medical conditions, such as chronic pain or substance use disorders. Both are persistent and/or relapsing conditions and are associated with complex treatment challenges and relatively poor outcomes in many patients. Substance use disorders frequently result in decreased quality of life; high levels of treatment resource requirements; the development of medical and psychiatric comorbidities, thereby increasing personal burdens and necessitating additional treatment costs; loss to the labour market; and offending behaviour to fund the acquisition of substances. The presence of chronic pain is associated with a similar range of personal, societal and economic burdens, with the exception of offending behaviour. Indeed, Breivik and colleagues (2013) reported that the personal and socioeconomic impact of chronic pain is at least equal to that of established priority healthcare issues such as cardiovascular disease and cancer. The effective management of substance use disorders and chronic pain, and of comorbid clinical populations, is key in alleviating personal suffering and the high social and economic burdens associated with these conditions. Understanding the complex treatment requirements of these comorbid clinical populations is necessarily more challenging due to the compounding effect of these conditions and the dynamic relationship between substance use disorders and chronic pain. A first step towards understanding the treatment requirements of these comorbid clinical populations is to profile the clinical characteristics of potential subgroups.

As discussed in the introductory chapter, chronic pain (CP) is associated with elevated morbidity and mortality and, in opioid replacement therapy (ORT) treatment populations, with a variety of poor ORT treatment outcomes. The current chapter begins by presenting an extensive cross-

sectional profile at study inception of the CP sample within an ORT treatment population in the East of Scotland. It then reports 5-year follow-up findings, focussing on core domains of relevance in the treatment of opioid-dependent patients: mortality; illicit substance use; and health.

3.1.1 Objectives

The first objective was to examine whether the group of patients excluded from the study cohort as a consequence of missing data differed to those included in the study cohort. The second objective was to profile the patient group with comorbid chronic pain in an ORT treatment population at study inception and to compare this group to ORT patients with no pain, to determine whether these two groups were similar or if they presented as clinically-distinct groups associated with specific treatment challenges. The third objective was to evaluate key ORT treatment outcomes over a 5-year follow-up period in the ORT group with comorbid chronic pain compared to the ORT group with no pain. Key ORT treatment outcomes focus on mortality, illicit substance use and health.

3.2 Representativeness of the study cohort compared with the clinical population

The first of the core objectives was to examine the representativeness of the study cohort compared with the entire treatment population. Participants were excluded if duration of pain at study inception was not recorded on the Brief Pain Inventory – Short Form (BPI-SF), or if no BPI-SF was completed, since it was not possible to determine if their pain was 'chronic'. Of the 626 patients in receipt of ORT in Tayside at study inception in 2005, 521 completed a modified version of the BPI-SF. The remaining 105 (17%) were, therefore, excluded from the study cohort. The battery of assessments undertaken at study inception was scheduled over a series of clinic appointments, therefore the absence of data generally signifies that patients did not attend that specific clinic appointment. It was, therefore, important to assess whether those that completed assessment instruments differed significantly from those that did not and, in consequence, an extensive range of demographic, socioeconomic and personal characteristics was examined. ***Tables 3.1a to 3.1d*** report the representativeness of the sample that comprises the study cohort compared with those that were excluded due to missing data.

Table 3.1a: *Representativeness of the study cohort of the overall cohort in treatment at study inception – demographic characteristics.*

Categorical variables	**Study cohort [n=521]**		**Missing data [n=105]**	
	N	**%**	**N**	**%**
Gender	***$\chi^2(1)=0.460$; p=0.497 (ω=0.027)***			
Male	360	69	67	66
Female	161	31	35	34
Deprivation status (SIMD*)	***$\chi^2(1)=28.805$; p<0.001 (ω=0.217)***			
Affluent	27	5	21	21
Deprived	487	95	79	79
Geographical area	***$\chi^2(2)=335.191$; p<0.001 (ω=0.735)***			
Angus	126	24	14	14
Dundee	372	72	10	10
Perth & Kinross	21	4	77	76
Urban – rural habitation	***$\chi^2(1)=12.847$; p<0.001 (ω=0.145)***			
Urban	465	91	79	79
Rural	45	9	21	21
Continuous variables	**Study cohort [n=521]**		**Missing data [n=105]**	
	$\bar{x}$	σ	$\bar{x}$	σ
Age (years)	***F(1,618)=1.654; p=0.199; η_p^2=0.003***			
	33	7.81	32	7.84

* Scottish Index of Multiple Deprivation (quintiles 1 and 2 indicate relative deprivation; quintiles 3-5 indicate relative affluence)

Table 3.1b: *Representativeness of the study cohort of the overall cohort in treatment at study inception – educational characteristics.*

	Study cohort [n=521]		**Missing data [n=105]**	
	N	**%**	**N**	**%**
Education level attained	***$\chi^2(4)=7.685$; p=0.104 (ω=0.114)***			
None	269	54	43	46
O grade / S grade	137	28	27	29
Apprenticeship / City and Guilds	12	2	0	0
Highers	22	4	5	5
College / university	59	12	19	20
Patient-rated literacy and numeracy skills	***$\chi^2(2)=0.086$; p=0.958 (ω=0.012)***			
Not good	52	10	9	9
OK	190	38	38	39
Good	263	52	50	52

Table 3.1c: *Representativeness of the study cohort of the overall cohort in treatment at study inception – home and family characteristics.*

	Study cohort [n=521]		Missing data [n=105]	
	N	**%**	**N**	**%**
Frequency of changing address	***$\chi^2(3)=2.247$; p=0.523 (ω=0.067)***			
Never	92	22	17	21
Sometimes	247	59	47	57
Frequently	65	16	17	21
Very frequently	14	3	1	1
Living circumstances (alone or with others)	***$\chi^2(2)=3.766$; p=0.152 (ω=0.078)***			
Alone	202	39	30	30
With others	304	59	66	66
Hostel	11	2	4	4

Table 3.1d: *Representativeness of the study cohort of the overall cohort in treatment at study inception – health and treatment characteristics.*

	Study cohort [n=521]		Missing data [n=105]	
	N	**%**	**N**	**%**
Patient-reported physical health problems	***$\chi^2(1)=10.634$; p=0.001 (ω=0.131)***			
No	257	50	68	67
Yes	261	50	33	33
Patient-reported mental health problems	***$\chi^2(1)=2.574$; p=0.109 (ω=0.064)***			
No	285	55	66	63
Yes	234	45	38	37
In receipt of support from other agencies	***$\chi^2(1)=1.248$; p=0.364 (ω=0.045)***			
No	386	75	79	80
Yes	132	25	20	20

3.2.1 Summary of section findings: Representativeness of the study cohort

The study cohort (n=521) was broadly representative of the entire treatment population (n=626) with very few significant differences between those that were included and those that were excluded due to an absence of BPI-SF data. A significantly greater proportion of those that were excluded due to missing data comprised patients were: relatively affluent; living in urban locations; and associated with fewer physical health problems. Furthermore, there was a

significant association with geographical location, and visual inspection suggested that significantly more patients were excluded from the Perth & Kinross local authority area.

3.3 Profile of patients with chronic pain in an ORT population

The second objective was to profile patients with chronic pain in an ORT treatment population and compared with patients in ORT with no pain. The section begins by identifying the subgroups with chronic pain and no pain and then focuses on characteristics of key importance in ORT treatment programmes at study inception (sociodemographic characteristics, illicit substance use, medical and psychiatric morbidity and treatment characteristics).

3.3.1 Identification chronic pain in the study cohort

Of the 521 patients that completed a full pain assessment, 300 (58%) reported pain at study inception; however, 54 of them indicated a pain duration of between 1 and 11 months and, therefore, did not meet the criteria for inclusion in either the chronic pain (CP) or the no pain (NoP) group. A breakdown of these findings is reported in ***Table 3.2***.

Table 3.2: *Proportion of the study cohort eligible for inclusion in the CP and NoP groups.*

	Number	Percent	Valid percent
Included in analyses			
Chronic pain (CP)	246	47	53
No pain (NoP)	221	42	47
Excluded from analyses			
Pain duration of 1-3 months	29	6	n/a
Pain duration of 4-11 months	25	5	n/a
Total	521	100	100

A total of 467 participants were included in the analyses: 246 (53%) in the chronic pain (CP) group and 221 (47%) in the no pain (NoP) group.

A modified version of the Brief Pain Inventory – Short Form (BPI-SF) was used to obtain information about pain experiences at study inception. Not all participants answered all questions; percentages were calculated in respect of the number having responded to each question. Patients with chronic pain reported a mean duration of pain of 99 months (SD=88; median=72; range=12-550). On a 0-100 scale these patients reported a mean pain intensity of 63 (SD=21; median=65; range=4-100). Almost a quarter (24%, n=58) were experiencing pain at multiple sites (i.e. two or more sites), 70% (n=173) reported pain interference in daily activities

and 80% (n=197) reported sleep interference. More than three quarters (79%, n=175) had attended a physician for treatment and, of those, 41% (n=75) were treated by a pain specialist. Just over half of those treated by a physician (59%, n=113) felt that their pain problem had been taken seriously. Just over half (56%, n=114) were in receipt of an analgesic prescription with 22% (n=45) of them having been in receipt of an opioid analgesic prescription, in addition to methadone prescribed as ORT for the treatment of opioid dependence..

3.3.2 Sociodemographic characteristics of patients with chronic pain and without pain at study inception

Sociodemographic characteristics at study inception are reported in ***Tables 3.3 to 3.5***.

Table 3.3: *Group differences in demographic characteristics at study inception.*

	CP		NoP	
	N	**%**	**N**	**%**
Gender	***$\chi^2(1)=1.644$; p=0.120 (ω=0.062)***			
Male	155	68	148	74
Female	73	32	53	26
Socioeconomic deprivation	***$\chi^2(4)=8.137$; p=0.087 (ω=0.134)***			
SIMD Quintile 1	163	68	124	58
SIMD Quintile 2	59	24	60	28
SIMD Quintile 3	13	5	18	8
SIMD Quintile 2	2	1	8	4
SIMD Quintile 5	5	2	4	2
Geographical area	***$\chi^2(2)=1.854$; p=0.396 (ω=0.066)***			
Angus	49	22	54	27
Dundee	171	75	139	69
Perth & Kinross	8	3	8	4
Urban-rurality	***$\chi^2(5)=4.651$; p=0.460 (ω=0.101)***			
Large urban areas	176	73	147	69
Other urban areas	46	19	49	23
Accessible small towns	9	4	13	6
Remote small towns	1	1	0	0
Accessible rural	7	3	4	2
Remote rural				
	CP		**NoP**	
	$\bar{x}$	σ	$\bar{x}$	σ
Age	***$F(1,428)=14.980$; p<0.001 (η_p^2=0.034)***			
	34.97	7.49	32.10	7.86

The two groups were very similar concerning demographic characteristics. Almost three quarters of each group were male and socioeconomic deprivation was identified in around 90% of each group. The CP group was statistically significantly older than the NoP group by a mean difference of just under 3 years. Median age was 35 years (range: 21-66 years) in the CP group and 31 years (range: 18-65 years) in the NoP group.

Table 3.4: *Group differences in education and employment characteristics at study inception (categorical variables).*

Categorical variables	**CP**		**NoP**	
	N	**%**	**N**	**%**
Educational attainment	***$\chi^2(4)=5.525$; p=0.238 (ω=0.116)***			
None	126	58	102	52
O' Grades	54	25	56	28
Apprentice/SVQ/City & Guilds	5	2	6	3
Highers	12	6	5	3
College/University	20	9	27	14
Literacy/numeracy skills	***$\chi^2(2)=2.175$; p=0.337 (ω=0.072)***			
'Not good'	28	13	17	9
'OK'	84	38	74	37
'Good'	108	49	107	54
Any paid work in past 30 days	***$\chi^2(1)=7861$; p=0.004 (ω=0.140)***			
Yes	13	6	27	14
No	202	94	160	86
Any work absence due to illness	***$\chi^2(1)=8.315$; p=0.004 (ω=0.456)***			
Yes	5	39	1	4
No	8	61	26	96
Unemployed in past 30 days	***$\chi^2(1)=0.024$; p=0.486 (ω=0.008)***			
Yes	166	79	142	78
No	45	21	40	22
	CP		**NoP**	
	$\bar{x}$	σ	$\bar{x}$	σ
Number of days employed in past 30 days	***F(1,39)=4.777; p=0.035 (η_p^2=0.112)***			
	16.77	13.15	23.85	7.41
Number of days' sick leave in past 30 days	***F(1,39)=4.591; p=0.039 (η_p^2=0.108)***			
	3.62	8.80	0.04	0.19

Whilst educational attainment was similar in both groups, a significantly smaller proportion of the CP group was in employment in the 30 days preceding assessment and a significantly higher proportion of this group was absent from work due to illness during this period. Furthermore, the CP group was significantly associated with fewer days' employment in the 30 days preceding assessment and with more days' absence from work due to illness.

Table 3.5: *Group differences in home and family characteristics at study inception (categorical variables).*

Categorical variables	**CP**		**NoP**	
	N	**%**	**N**	**%**
Frequency of changing address	***$\chi^2(3)=5.682$; p=0.128 (ω=0.128)***			
Never	47	26	28	17
Sometimes	103	56	113	68
Frequently	28	15	22	13
Very frequently	5	3	3	2
Time at current address	***$\chi^2(5)=6.679$; p=0.246 (ω=0.125)***			
< 1 month	11	5	9	5
1-6 months	21	9	25	12
6-12 months	35	16	25	12
1-3 years	56	25	62	31
3-5 years	39	17	21	11
5+ years	63	28	58	29
Lives alone or with others	***$\chi^2(4)=3.139$; p=0.535 (ω=0.086)***			
Alone	87	38	75	38
With partner	50	22	46	23
With family	80	35	64	32
With friends	9	4	11	5
Hostel	1	1	4	2
Has children	***$\chi^2(1)=9.540$; p=0.002 (ω=0.153)***			
Yes	186	86	138	73
No	31	14	50	27
Children live at home	***$\chi^2(1)=0.095$; p=0.423 (ω=0.017)***			
Yes	86	48	67	49
No	95	52	69	51

The two groups were very similar concerning residential stability and living circumstances. A significantly higher proportion of the CP group had children; however, the majority of both groups had children.

3.3.3 Illicit substance use in patients with and without chronic pain at study inception

Illicit substance use at study inception is reported in ***Table 3.6a*** (categorical dependent variables) and ***Table 3.6b*** (continuous dependent variables).

Table 3.6a: *Group differences in patient-reported substance use in the 28 days prior to study inception and biochemical drug screen results at study inception (categorical variables). Prescription medication was controlled in analyses of biochemical drug screen results.*

	CP		NoP	
	N	**%**	**N**	**%**
Any illicit drug use reported	***$\chi^2(1)=3.310$; p=0.050 (ω=0.091)***			
Yes	200	93	164	88
No	15	7	23	12
Illicit heroin use reported	***$\chi^2(1)=3.283$; p=0.044 (ω=0.090)***			
Yes	86	40	92	49
No	128	60	95	51
Illicit methadone use reported	***$\chi^2(1)=0.701$; p=0.232 (ω=0.042)***			
Yes	73	34	71	38
No	142	66	116	62
Illicit opioid analgesics use reported	***$\chi^2(1)=0.045$; p=0.831 (ω=0.010)***			
Yes	34	16	29	16
No	179	84	158	85
Illicit diazepam use reported	***$\chi^2(1)=0.029$; p=0.475 (ω=0.008)***			
Yes	73	34	62	33
No	142	66	125	67
Illicit cannabis use reported	***$\chi^2(1)=8.037$; p=0.003 (ω=0.142)***			
Yes	172	81	128	68
No	41	19	59	32
Positive biochemistry opioid results	***$\chi^2(1)=2.537$; p=0.067 (ω=0.076)***			
Yes	106	47	114	55
No	120	53	95	45
Positive biochemistry benzodiazepine results	***$\chi^2(1)=5.062$; p=0.016 (ω=0.108)***			
Yes	153	69	121	58
No	70	31	87	42
Positive biochemistry cannabinoid results	***$\chi^2(1)=4.720$; p=0.025 (ω=0.210)***			
Yes	46	84	34	65
No	9	16	18	35

Whilst the majority of both groups reported illicit substance use, illicit use of any substances was marginally significantly higher in the CP group. Of the specific drugs examined, a significantly higher proportion of the CP reported illicit cannabinoid use. Biochemical drug screens corroborated this finding and also revealed a significantly higher proportion of non-medical use of benzodiazepines in this group. Conversely, a significantly higher proportion of the NoP group reported illicit use of heroin.

Table 3.6b: *Group differences in patient-reported substance use at study inception (continuous variables).*

Continuous variables	**CP**		**NoP**	
	$\bar{x}$	σ	$\bar{x}$	σ
Days heroin use in past 30 days	***F(1,400)=7.307; p=0.007 (η_p^2=0.018)***			
	3.30	7.30	5.58	9.51
Days methadone use in past 30 days	***F(1,401)=1.951; p=0.163 (η_p^2=0.005)***			
	3.30	7.84	4.48	9.01
Days other opioid use in past 30	***F(1,399)=0.353; p=0.553 (η_p^2=0.001)***			
	0.62	2.68	0.81	3.47
Days benzodiazepine use in past 30	***F(1,401)=0.001; p=0.978 (η_p^2=0.000)***			
	3.07	7.56	3.09	7.38
Days cannabis use in past 30 days	***F(1,299)=4.219; p=0.041 (η_p^2=0.014)***			
	23.29	10.45	20.63	11.96

The NoP group was associated with a significantly higher number of days' use in the 30 days preceding assessment; whereas, the CP group was associated with a significantly higher number of days' use of cannabinoids.

3.3.4 Medical morbidity in patients with and without chronic pain at study inception

A significantly higher proportion of the CP group (69% compared with 39% in the NoP group) reported physical health problems at study inception ($\chi^2(1)=34.826$; $p<0.001$; $\omega=0.298$). The CP group was associated with a significantly higher score (17.13 (7.66) compared with 10.19 (6.81) in the NoP group) on the MAP Physical Health subscale ($F(1,459)=104.36$; $p<0.001$ ($\eta_p^2=0.186$)). The individual items comprising the subscale are reported in ***Table 3.7***.

Table 3.7: *Group differences at study inception in the MAP physical health subscale items.*

Individual subscale items	CP		NoP	
	N	%	N	%
Poor appetite	***$\chi^2(2)=18.070$; $p<0.001$ ($\omega=0.197$)***			
Never	32	13	57	26
Rarely/sometimes	81	33	83	37
Often/always	132	54	81	37
Tiredness or fatigue	***$\chi^2(2)=22.542$; $p<0.001$ ($\omega=0.220$)***			
Never	33	13	53	24
Rarely/sometimes	85	35	100	45
Often/always	127	52	68	31
Nausea	***$\chi^2(2)=13.484$; $p=0.001$ ($\omega=0.170$)***			
Never	99	41	125	57
Rarely/sometimes	91	37	68	31
Often/always	54	22	28	12
Stomach pain	***$\chi^2(2)=20.686$; $p<0.001$ ($\omega=0.211$)***			
Never	69	28	91	41
Rarely/sometimes	100	41	98	45
Often/always	76	31	31	14
Breathing difficulties	***$\chi^2(2)=32.729$; $p<0.001$ ($\omega=0.265$)***			
Never	87	35	135	61
Rarely/sometimes	102	42	65	29
Often/always	55	23	21	10
Chest pain	***$\chi^2(2)=59.106$; $p<0.001$ ($\omega=0.357$)***			
Never	102	42	170	77
Rarely/sometimes	108	44	37	17
Often/always	34	14	14	6
Joint or bone pain	***$\chi^2(2)=110.050$; $p<0.001$ ($\omega=0.487$)***			
Never	47	19	137	62
Rarely/sometimes	84	35	64	29
Often/always	112	46	20	9
Muscle pain	***$\chi^2(2)=52.396$; $p<0.001$ ($\omega=0.335$)***			
Never	78	32	129	58
Rarely/sometimes	84	34	73	33
Often/always	83	34	19	9
Numbness or tingling	***$\chi^2(2)=56.462$; $p<0.001$ ($\omega=0.348$)***			
Never	77	31	144	66
Rarely/sometimes	95	39	52	24
Often/always	73	30	24	11
Tremors or shakes	***$\chi^2(2)=20.549$; $p<0.001$ ($\omega=0.210$)***			
Never	96	39	132	60
Rarely/sometimes	102	42	64	29
Often/always	47	19	24	11

NOTE 1: The range of the MAP physical health subscale score is 0-40.

NOTE 2: The alpha was adjusted to control for multiple testing on the individual subscale items – the subscale comprised ten items, therefore, statistical significance was indicated by $p \leq 0.005$.

The CP group was associated with a significantly higher mean physical health subscale score (possible range of 0-40). This subscale is problem-scored, therefore, a higher score is indicative of poorer physical health. Furthermore, after adjusting the alpha for multiple testing on the individual subscale items, a significantly higher proportion of the CP group was associated more frequent presence of each of the individual subscale symptoms.

3.3.5 Psychiatric morbidity in patients with and without chronic pain at study inception

Psychiatric morbidity at study inception is reported in ***Tables 3.8 to 3.10***. ***Table 3.8a*** shows the prevalence of psychiatric 'caseness' and ***Table 3.8b*** shows psychiatric symptom severity in each group. ***Table 3.9a*** shows the prevalence of neurotic disorders and symptoms and ***Table 3.9b*** shows the severity of neurotic disorders in each group. ***Table 3.10a*** shows the prevalence of mood symptoms and ***Table 3.10b*** shows the severity of mood disorders in each group. The alpha was adjusted to control for multiple testing on the individual MAP subscale items – the subscale comprised ten items (5 anxiety-related symptoms and 5 mood-related symptom); therefore, statistical significance was indicated in each group of responses by $p \leq 0.010$.

Table 3.8a: *Group differences in prevalence of psychiatric morbidity at study inception.*

	CP		NoP	
	N	**%**	**N**	**%**
Self-reported mental health problems	***$\chi^2(1)=3.651$; $p=0.035$ ($\omega=0.100$)***			
Yes	104	52	71	42
No	95	48	97	58
Psychiatric 'caseness' on the GHQ-28	***$\chi^2(1)=9.781$; $p=0.001$ ($\omega=0.159$)***			
Yes	126	62	84	46
No	78	38	99	54
CORE clinical score categories	***$\chi^2(1)=12.354$; $p<0.001$ ($\omega=0.165$)***			
Clinical range (10-40)	175	74	127	58
Non-clinical (0-9)	62	26	91	42

Table 3.8b: *Group differences in severity of general psychiatric morbidity at study inception.*

	CP		NoP	
	$\bar{x}$	σ	$\bar{x}$	σ
MAP mental health subscale score	***F(1,460)=24.869; p<0.001 (η_p^2=0.051)***			
	17.93	9.35	13.79	8.40
GHQ-28 subscale scores				
Social Dysfunction	***F(1,443)=4.978; p=0.026 (η_p^2=0.011)***			
	8.27	3.24	7.62	2.95
CORE subscale scores				
Subjective Wellbeing	***F(1,454)=5.485; p=0.020 (η_p^2=0.012)***			
	7.39	4.48	6.47	3.85
Problems/Symptoms	***F(1,454)=26.260; p<0.001 (η_p^2=0.055)***			
	25.68	17.44	18.66	10.68
Life Functioning	***F(1,454)=9.021; p=0.003 (η_p^2=0.020)***			
	18.94	11.88	15.90	9.47
Risk/Harm	***F(1,454)=5.123; p=0.024 (η_p^2=0.011)***			
	2.55	3.67	1.83	3.07

NOTE: The range of the MAP mental health subscale score is 0-40; the range of the GHQ-28 social dysfunction subscale score is 0-21; the range of the CORE subjective wellbeing subscale score is 0-16; the range of the CORE problems/symptoms and life functioning subscale scores is 0-48; the range of the CORE risk/harm subscale score is 0-24.

The CP group reported a significantly higher prevalence of mental health problems, and this finding was corroborated by standardised testing using both the GHQ-28 and the CORE. The MAP mental health subscale is problem-scored, therefore, the significantly higher mean score in the CP group is indicative of poorer general psychiatric health. The CP group was associated with significantly higher mean scores on all of the general psychiatric wellbeing and functioning subscales of the GHQ-28 and the CORE. The subjective wellbeing and life functioning subscales of the CORE are problem-scored, indicating poorer health in the CP group.

Table 3.9a: *Group differences in prevalence of neurotic disorders and symptoms at study inception.*

	CP		NoP	
	N	**%**	**N**	**%**
Social phobia 'caseness' [SPDQ]	***$\chi^2(1)=3.350$; p=0.042 (ω=0.092)***			
Yes	94	44	65	35
No	120	56	121	65
PTSD caseness [IES]	***$\chi^2(1)=5.222$; p=0.014 (ω=0.107)***			
Yes	98	41	66	30
No	144	59	152	70
MAP mental health subscale questions relating to anxiety symptoms				
Feeling tense	***$\chi^2(2)=16.411$; p<0.001 (ω=0.188)***			
Never	25	10	38	17
Rarely / sometimes	87	36	104	47
Often / always	132	54	79	36
Suddenly scared for no reason	***$\chi^2(2)=24.990$; p<0.001 (ω=0.232)***			
Never	64	26	93	42
Rarely / sometimes	86	35	86	39
Often / always	94	39	41	19
Feeling fearful	***$\chi^2(2)=26.074$; p<0.001 (ω=0.228)***			
Never	65	27	89	40
Rarely / sometimes	88	36	94	43
Often / always	90	37	38	17
Nervousness or shakiness	***$\chi^2(2)=18.836$; p<0.001 (ω=0.201)***			
Never	46	19	66	30
Rarely / sometimes	100	41	105	48
Often / always	98	40	49	22
Terror or panic	***$\chi^2(2)=26.841$; p<0.001 (ω=0.240)***			
Never	88	36	126	57
Rarely / sometimes	86	35	68	31
Often / always	70	29	27	12

Table 3.9b: *Group differences in severity of neurotic disorders at study inception.*

	CP		NoP	
	$\bar{x}$	σ	$\bar{x}$	σ
GHQ-28 subscales				
Somatic Symptoms	***F(1,445)=38.305; p<0.001 (η_p^2=0.079)***			
	8.03	3.83	5.87	3.52
Anxiety/Insomnia	***F(1,445)=12.954; p<0.001 (η_p^2=0.028)***			
	8.81	4.86	7.22	4.38
PTSD subscales [IES]				
Intrusion	***F(1,459)=11.321; p=0.001 (η_p^2=0.024)***			
	12.26	13.81	8.47	11.60
Avoidance	***F(1,459)=4.827; p=0.029 (η_p^2=0.010)***			
	12.81	13.95	10.06	12.72
	CP		**NoP**	
	N	**%**	**N**	**%**
Severity of PTSD [IES]	***χ^2(3)=11.060; p=0.011 (ω=0.155)***			
Subclinical	113	47	124	57
Mild	14	6	14	6
Moderate	34	14	37	17
Severe	81	33	43	20

NOTE: The range of the GHQ-28 subscale scores is 0-21; the range of the IES intrusion subscale score is 0-35; and the range of the IES avoidance subscale score is 0-40.

A significantly higher prevalence of social phobia and posttraumatic stress disorder (PTSD) was found in the CP group and a significantly higher proportion of the CP group was associated with more frequent presence of each of the individual MAP mental health subscale symptoms. The CP group was associated with significantly higher mean subscale scores on both the somatic symptoms and anxiety/insomnia subscales of the GHQ-28. A significantly higher proportion of the CP group was associated with severe PTSD and the CP group was associated with significantly higher mean scores on both the intrusion and avoidance PTSD subscales.

Table 3.10a: *Group differences in prevalence of mood symptoms at study inception.*

	CP		NoP	
	N	**%**	**N**	**%**
MAP mental health subscale questions relating to depressive symptoms				
Feeling hopeless	***$\chi^2(2)=3.643$; p=0.162 (ω=0.089)***			
Never	54	22	63	29
Rarely / sometimes	112	46	102	46
Often / always	78	32	56	25
Worthlessness	***$\chi^2(2)=6.456$; p=0.040 (ω=0.118)***			
Never	53	22	69	31
Rarely / sometimes	109	45	96	63
Often / always	81	33	56	25
No interest in things	***$\chi^2(2)=5.687$; p=0.058 (ω=0.111)***			
Never	54	22	54	24
Rarely / sometimes	94	36	103	47
Often / always	96	39	64	29
Feeling lonely	***$\chi^2(2)=9.987$; p=0.007 (ω=0.147)***			
Never	70	29	81	37
Rarely / sometimes	97	40	98	44
Often / always	77	32	42	19
Suicidal thoughts	***$\chi^2(2)=6.969$; p=0.031 (ω=0.123)***			
Never	172	70	170	77
Rarely / sometimes	56	23	46	21
Often / always	16	7	4	2

Table 3.10b: *Group differences in severity of mood disorders at study inception.*

Continuous variables	**CP**		**NoP**	
	$\bar{x}$	σ	$\bar{x}$	σ
GHQ-28 subscales				
Severe Depression	***$F(1,442)=5.928$; p=0.015 (η_p^2=0.013)***			
	5.07	4.87	4.03	4.09

The CP group was associated with a significantly higher mean score on the severe depression subscale of the GHQ-28; however, after adjusting the alpha for multiple testing, only one symptom from the MAP mental health subscale items (feeling lonely) was found to be statistically significant.

3.3.6 ORT treatment characteristics in patients with and without chronic pain at study inception

Group differences in ORT treatment characteristics are shown in ***Table 3.11***. Prescribing information was recorded using the Maudsley Addiction Profile (MAP) and the ORT treatment perception score was obtained by summing the individual items on the Treatment Perception Questionnaire (TPQ). Since diazepam is a commonly-prescribed treatment in ORT programmes, it was examined in addition to mean methadone dose.

Table 3.11: *Group differences in ORT treatment characteristics at study inception.*

	CP		NoP	
	N	**%**	**N**	**%**
Diazepam prescription	***$\chi^2(1)=8.233$; p=0.003 (ω=0.133)***			
Yes	90	37	54	24
No	155	63	167	76
Analgesic diazepam prescription	***Not computed***			
Yes	3	2	0	0
No	201	98	221	100
	CP		**NoP**	
	$\bar{x}$	σ	$\bar{x}$	σ
Mean methadone dose	***F(1,419)=4.370; p=0.037 (η_p^2=0.010)***			
	54.75	24.28	25.29	24.85
Mean diazepam dose	***F(1,143)=2.435; p=0.121 (η_p^2=0.017)***			
	25.92	13.89	22.07	15.03
Mean ORT treatment perception score	***F(1,439)=7.034; p=0.008 (η_p^2=0.016)***			
	21.82	6.20	23.33	5.63

The CP group was in receipt of a significantly higher mean daily methadone dose at study inception. A significantly higher proportion of the CP group was in receipt of a diazepam prescription at study inception and a negligibly small proportion of this group (2%) was in receipt of diazepam for pain management (prescribed by TSMS and reported to be specifically for pain management). The mean ORT treatment perception score indicates that the CP group was significantly less satisfied with treatment.

3.3.7 Summary of section findings: Clinical profile of opioid-dependent patients with comorbid chronic pain at study inception

The findings of the current sections suggest that ORT patients with comorbid chronic pain present as a clinically-distinct group compared with ORT patients with no pain, and that the presence of comorbid chronic pain in this treatment population is associated with specific treatment challenges. Whilst sociodemographic characteristics were very similar in both groups, a smaller proportion of the CP group was in employment and, among those in employment, work interference due to illness was more evident compared with the NoP group. The CP group was significantly associated with problematic benzodiazepine and cannabinoid use in contrast to the NoP group, which was significantly associated with problematic heroin use. It should be noted, however, that, despite elevated heroin use in the NoP group, a substantial proportion of the CP group also reported illicit heroin use. The CP group was consistently associated with elevated medical morbidity and with psychiatric morbidity, including general functioning, neurotic disorders and severe depression. The CP group was significantly associated with a higher mean methadone dose and with elevated prescription diazepam use, a commonly-prescribed treatment in ORT settings. Despite being in receipt of more treatment than the NoP group, the CP group expressed more ORT treatment dissatisfaction. These findings highlight that, whilst these two groups have similar sociodemographic profiles, the CP group is associated with elevated morbidity and with a clinically-distinct substance use profile, and suggest that the CP group presents as a more challenging treatment population.

3.4 Five-year follow-up of core ORT treatment outcomes

The third objective was to evaluate key ORT treatment outcomes over a 5-year follow-up period in the ORT group with comorbid chronic pain compared to the ORT group with no pain. Findings are reported in sections: 3.4.1 (mortality); 3.4.2 (illicit substance use); 3.4.3 (physical morbidity); and 3.4.4 (psychiatric morbidity).

3.4.1 Mortality during the 5-year follow-up period

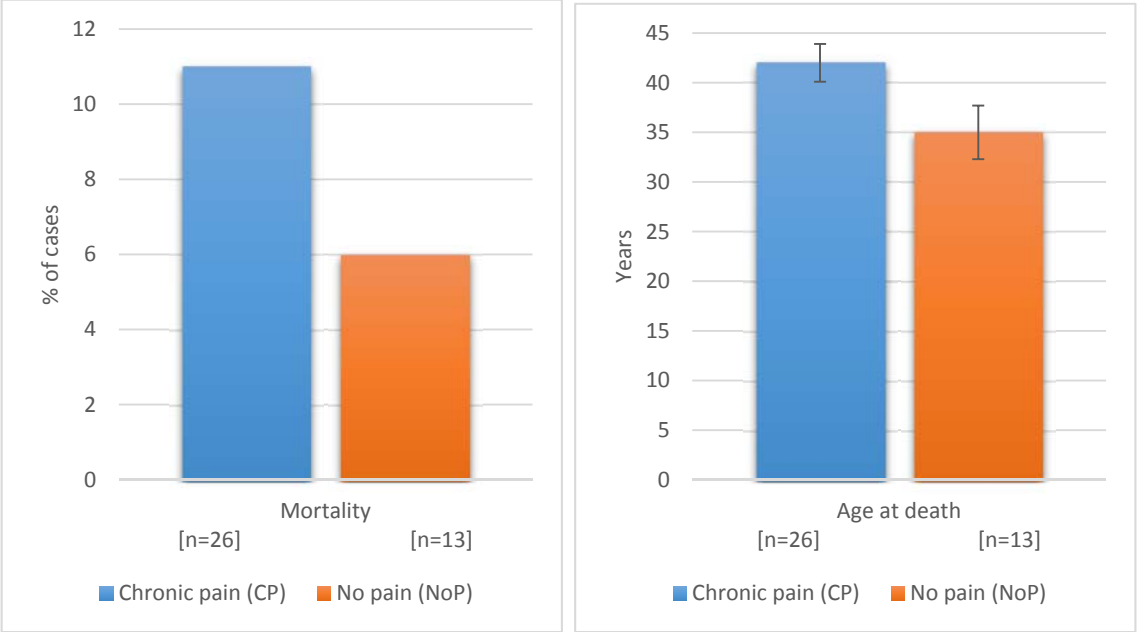


Figure 3.1: *Prevalence of mortality in the cohort (N=467) during the 5-year follow-up period and mean age at time of death. Error bars indicate standard error.*

A significantly higher proportion of the CP group was deceased at 5-year follow-up ($\chi^2(1)=3.341$; $p=0.047$; $\omega=0.085$). More than a tenth of the CP group (11%) died within the observation period as compared with 6% of the NoP group. There was no significant group difference concerning age at time of death.

There were a limited number of implicated causes of death in the population and they are reported in ***Figure 3.2***. In some cases more than one cause of death was implicated.

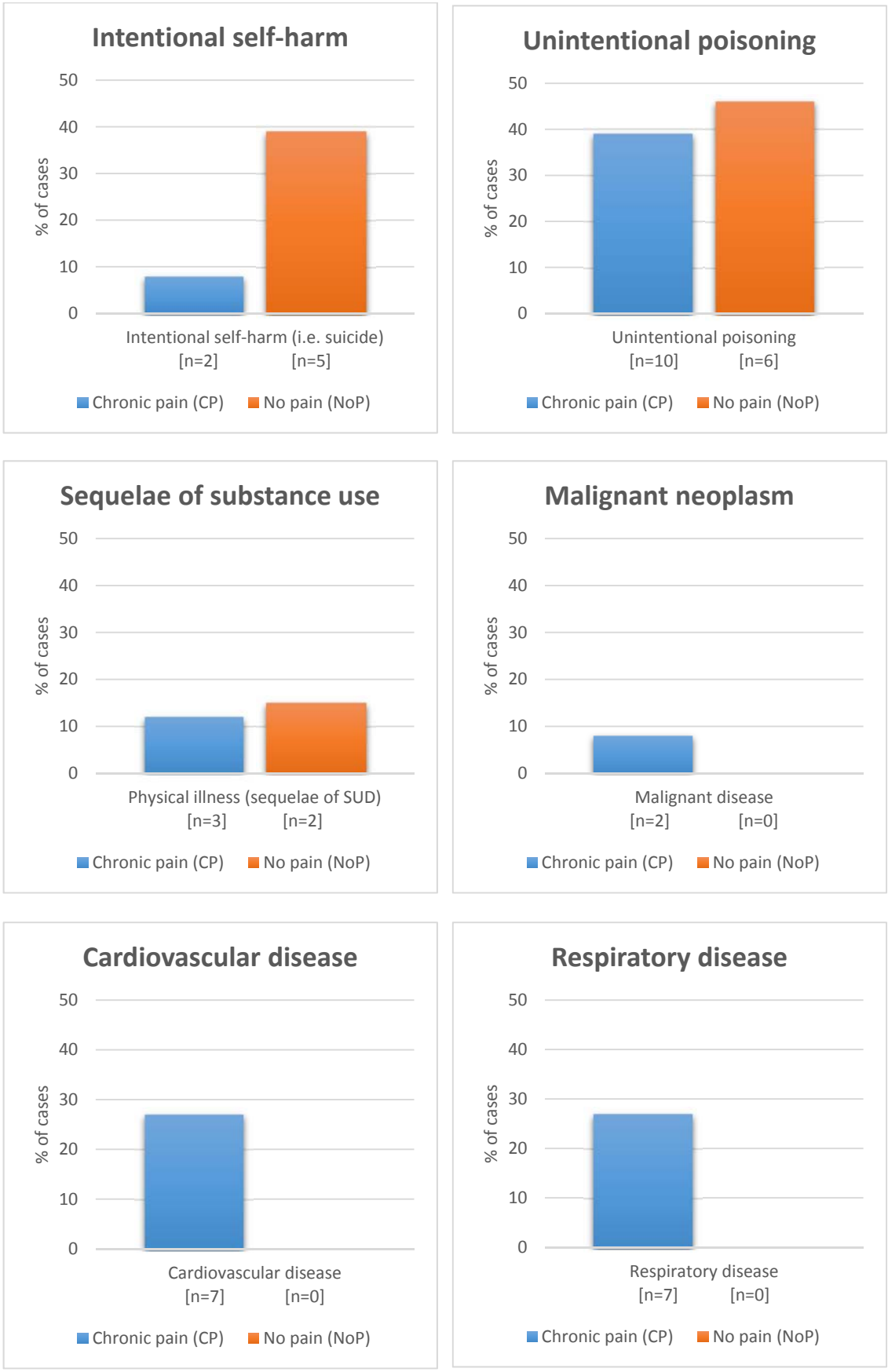


Figure 3.2: *Implicated causes of death in the cohort. More than one implicated cause applies in some cases.*

Intentional self-harm (i.e. suicide) was recorded as being implicated in a significantly higher proportion of deaths the NoP group ($\chi^2(1)=5.571$; $p=0.030$; $\omega=0.378$). More than a third of deaths in the NoP group were recorded as suicide (39%) as compared with 8% in the CP group. Both cases in the CP group died as a result of intentional poisoning. One case in the NoP group died as a result of drowning, one died as a result of asphyxiation and the remaining three cases died as a result of intentional poisoning.

Unintentional poisoning (i.e. accidental overdose) was implicated in almost half of the deaths in the NoP group (46%) and over a third of the deaths in the CP group (39%). There was no significant effect of group. ***Figure 3.2a*** shows that opioids were the most prevalent drug present on toxological analyses at time of death in both groups and that benzodiazepines and antidepressants were also identified in both groups. Opioids were more prevalent in the NoP group than the CP group and, in particular, heroin, which was more than twice as prevalent in the NoP group.

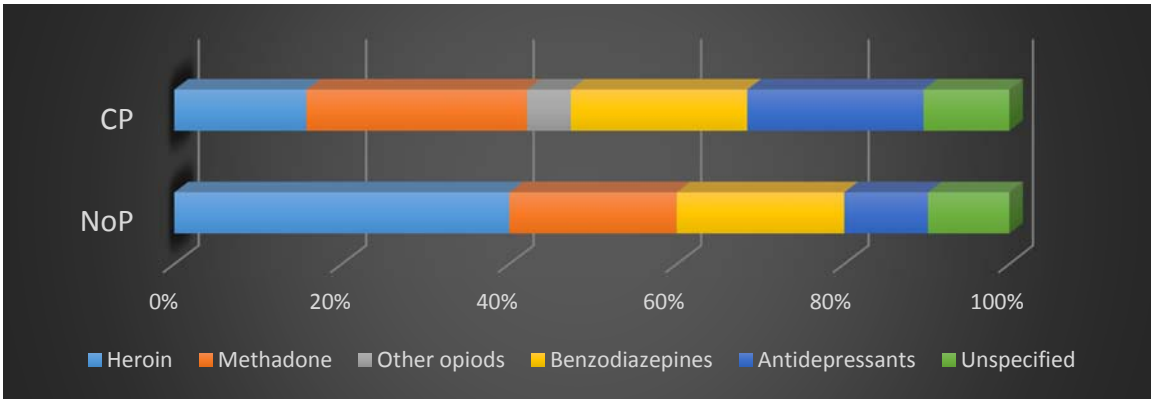


Figure 3.2a: *Percentage of patients with specific drugs present in toxological analyses at time of death following unintentional poisoning. Most patients had multiple drugs present in their system at death. The x-axis represents the spread of drugs across the two groups; therefore, the upper limit indicates 100% of drugs found on toxicology and not 100% of participants.*

There was no significant group difference regarding sequelae of substance misuse. Physical illness resulting from sequelae of substance use was implicated in 11% (n=3) of deaths in the CP group and 15% (n=2) of deaths in the NoP group. Alcoholic liver disease was implicated in both deaths in the NoP group; in one case the sequela was reported to be pulmonary oedema and, in the other case it was reported to be liver cirrhosis. Sequelae of opioid dependence were reported to be implicated in two of the three cases in the CP group (cardiovascular disease) and sequelae of alcohol dependence (liver cirrhosis) in the remaining case.

Malignant neoplasm was implicated in 8% of deaths in the CP group and none in the NoP group. There was no significant effect of group. One of the two cases was reported to have had malignant disease in the lung whilst the other had malignant disease in breast tissue.

There was a significant group difference concerning both cardiovascular disease and respiratory disease (both at $\chi^2(1)=4.266$; $p=0.043$; $\omega=0.331$). Although they were not the same cases, 27% of the CP group were recorded as having each of these diseases implicated in death as compared with none in the NoP group.

3.4.2 Illicit substance use during the 5-year follow-up period

The findings of biochemical drug screens at study inception and at 5-year follow-up are reported in ***Table 3.13a***. Whilst findings at study inception were reported previously, they are also included here for comparison with follow-up findings. In the absence of repeated measures statistical tests for binary data, chi square was used to analyse change in results between study inception and follow-up. Continuation and initiation of illicit drug use were considered independently of one another since initiation of illicit drug use after commencing treatment is consididered to be interesting, in a different way, to continuation of illicit drug use despite treatment. Continuation of illicit drug use was compared to cessation during the follow-up period, and initiation of illicit drug use was compared to no use at study inception or at follow-up. These findings are reported in ***Table 3.13b***.

It should be noted that drug screen results at follow-up were available only for those retained in ORT treatment at that point. Almost two thirds of the CP were retained in treatment at follow-up (65%, n=160), 26 cases (11%) were deceased and the remaining 60 cases (24%) were no longer in treatment. Just under half of the NoP group were retained in treatment at follow-up (48%, n=105), 13 cases (6%) were deceased and the remaining 103 cases (46%) were no longer in treatment.

Table 3.13a: *Biochemistry drug screen results by group at study inception and 5-year follow-up.*

Biochemistry results for illicit substance use (study inception and follow-up reported separately)	**CP**		**NoP**	
	N	**%**	**N**	**%**
Opioid results at inception	***$\chi^2(1)=2.537$; $p=0.067$ ($\omega=0.076$)***			
Positive	106	47	114	55
Negative	120	53	95	45
Benzodiazepine results at inception	***$\chi^2(1)=5.062$; $p=0.016$ ($\omega=0.108$)***			
Positive	153	69	121	58
Negative	70	31	87	42
Cannabinoid results at inception	***$\chi^2(1)=4.720$; $p=0.025$ ($\omega=0.210$)***			
Positive	46	84	34	65
Negative	9	16	18	35
Opioid results at 5-year follow-up	***$\chi^2(1)=0.538$; $p=0.304$ ($\omega=0.076$)***			
Positive	14	30	17	37
Negative	33	70	29	63
Benzodiazepine results at 5-year follow-up	***$\chi^2(1)=6.848$; $p=0.008$ ($\omega=0.284$)***			
Positive	34	74	18	46
Negative	12	26	21	54
Cannabinoid results at 5-year follow-up	***$\chi^2(1)=7.432$; $p=0.006$ ($\omega=0.277$)***			
Positive	34	68	19	40
Negative	16	32	28	60

Table 3.13b: *Changes in biochemical drug screen results between study inception and 5-year follow-up.*

Biochemistry results for illicit substance use	**CP**		**NoP**	
	N	**%**	**N**	**%**
Opioids: positive results at inception	***$\chi^2(1)=5.237$; p=0.027 (ω=0.411)***			
Continuation of use during the follow-up period	5	36	13	77
Cessation of use during the follow-up period	9	64	4	23
Benzodiazepines: positive results at inception	***$\chi^2(1)=4.268$; p=0.037 (ω=0.289)***			
Continuation of use during the follow-up period	19	70	10	42
Cessation of use during the follow-up period	8	30	14	58
Cannabinoids: positive results at inception	***$\chi^2(1)=9.692$; p=0.002 (ω=0.679)***			
Continuation of use during the follow-up period	8	100	4	31
Cessation of use during the follow-up period	0	0	9	69
Opioids: negative results at inception	***$\chi^2(1)=0.134$; p=0.459 (ω=0.047)***			
Initiation of use during the follow-up period	15	45	11	41
No use at study inception or follow-up	18	55	16	59
Benzodiazepines: negative results at inception	***$\chi^2(1)=2.694$; p=0.103 (ω=0.290)***			
Initiation of use during the follow-up period	14	78	7	50
No use at study inception or follow-up	4	22	7	50
Cannabinoids: negative results at inception	***Not computed***			
Initiation of use during the follow-up period	0	0	0	0
No use at study inception or follow-up	2	100	1	100

Since biochemical data were available for so few participants, particularly at follow-up, a replication of the analyses of biochemical drug screen results was undertaken using patient-reported measures and these findings are reported in ***Tables 3.14a and 3.14b***. Patient-reported findings were obtained through use of the Maudsley Addiction Profile (MAP) at study inception and the corresponding Treatment Outcome Profile (TOP) at follow-up; however, there was a substantial degree of missing data at follow-up. The TOP was completed during routine clinical appointments during the follow-up period and there are two likely reasons for absence of TOP data. First, clinicians may have had insufficient time within routine clinical appointments to complete all follow-up assessment paperwork due to other clinical issues; therefore, absence of TOP data may be random or may reflect enhanced clinical complexity or severity within this sub-population. Secondly, the absence of TOP data may reflect a failure of these patients to attend appointments and, since attempts to collect follow-up data were scheduled to have taken place over a series of routine clinical appointments, the absence of data may indicate a sub-population that routinely fails to attend appointments.

Table 3.14a: *Patient-reported drug use by group at study inception and five-year follow-up. Findings from study inception are reported in the first half of the table and 5 year follow-up findings are reported in the second half of the table.*

Biochemistry results for illicit substance use (study inception and follow-up reported separately)	**CP**		**NoP**	
	N	**%**	**N**	**%**
Opioid use at inception	***$\chi^2(1)=3.489$; p=0.038 (ω=0.087)***			
Illicit use reported	103	42	112	51
No illicit use reported	142	58	109	49
Benzodiazepine use at inception	***$\chi^2(1)=0.143$; p=0.390 (ω=0.018)***			
Illicit use reported	85	35	73	33
No illicit use reported	160	65	148	67
Cannabinoid use at inception	***$\chi^2(1)=8.846$; p=0.002 (ω=0.138)***			
Illicit use reported	199	82	155	70
No illicit use reported	44	18	66	30
Opioid use at follow-up	***$\chi^2(1)=0.003$; p=0.540 (ω=0.004)***			
Illicit use reported	34	33	32	33
No illicit use reported	68	67	65	67
Benzodiazepine use at follow-up	***$\chi^2(1)=0.968$; p=0.200 (ω=0.070)***			
Illicit use reported	47	46	38	39
No illicit use reported	55	54	59	61
Cannabinoid use at follow-up	***$\chi^2(1)=7.432$; p=0.006 (ω=0.277)***			
Illicit use reported	59	58	48	50
No illicit use reported	43	42	49	50

Table 3.14b: *Changes in patient-reported drug use between study inception and 5-year follow-up.*

Biochemistry results for illicit substance use at 5-year follow-up	**CP**		**NoP**	
	N	**%**	**N**	**%**
Opioids: positive results at study inception	***$\chi^2(1)=0.085$; p=0.463 (ω=0.029)***			
Continuation of use during the follow-up period	25	51	26	48
Cessation of use during the follow-up period	24	49	28	52
Benzodiazepines: positive results at inception	***$\chi^2(1)=0.733$; p=0.255 (ω=0.084)***			
Continuation of use during the follow-up period	25	51	23	43
Cessation of use during the follow-up period	24	49	31	57
Cannabinoids: positive results at inception	***$\chi^2(1)=0.123$; p=0.440 (ω=0.035)***			
Continuation of use during the follow-up period	28	57	29	54
Cessation of use during the follow-up period	21	43	25	46
Opioids: negative results at study inception	***$\chi^2(1)=0.038$; p=0.540 (ω=0.020)***			
Initiation of use during the follow-up period	8	15	6	14
No use at study inception or follow-up	44	85	37	86
Benzodiazepines: negative results at inception	***$\chi^2(1)=0.546$; p=0.300 (ω=0.076)***			
Initiation of use during the follow-up period	22	42	15	35
No use at study inception or follow-up	30	58	28	65
Cannabinoids: negative results at inception	***$\chi^2(1)=1.719$; p=0.135 (ω=0.135)***			
Initiation of use during the follow-up period	30	58	19	44
No use at study inception or follow-up	22	42	24	56

There were no group differences concerning illicit opioid use at study inception or at follow-up. Whilst there were no group differences in illicit opioid use, the proportion of the NoP group misusing opioids declined significantly during the observation period whilst misuse in the CP group did not differ significantly over time. A significantly higher proportion of the CP group was engaged in illicit cannabinoid use and non-medical benzodiazepine use at both study inception and follow-up. Benzodiazepine use did not differ in either group over time. The proportion of the CP group using cannabinoids declined significantly during the observation period whilst use in the NoP group did not differ significantly over time. Within the CP group, receipt of prescribed analgesia was significantly associated with increased positive benzodiazepine and cannabinoid drug screen results.

3.4.2.1 Predictive capacity of changes in therapeutic opioid dose on initiation and continuation of illicit drug use during the follow-up period

The impact of changes in opioid treatment (opioid analgesic dose, ORT dose and total opioid dose) during the follow-up period was examined using binary logistic regression. ***Table 3.15*** shows the associations between increased therapeutic opioid dose and initiation and continuation of illicit drug use.

Table 3.15: *Associations between increases in prescribed opioid dose and pattern of illicit drug use (assessed by biochemical drug screens) between study inception and follow-up.*

Change in therapeutic opioid dose between inception and follow-up		Likelihood of pattern of illicit drug use between inception and follow-up overall and by pain category		
		CP	NoP	Overall
		Initiation of illicit opioid use (n=118)		
Increased opioid analgesic dose	No (n=17)	1.00	Insufficient data	1.00
	Yes (n=27)	2.46 (0.59-10.3)	Insufficient data	1.47 (0.42-5.13)
Increased ORT dose	No (n=54)	1.00	1.00	1.00
	Yes (n=64)	1.62 (0.62-4.23)	0.64 (0.12-3.46)	1.26 (0.55-2.88)
Increased total opioid dose	No (n=54)	1.00	1.00	1.00
	Yes (n=64)	2.06 (0.78-5.43)	0.92 (0.19-4.54)	1.64 (0.72-3.75)
		Continued illicit opioid use (n=130)		
Increased opioid analgesic dose	No (n=10)	1.00	Insufficient data	1.00
	Yes (n=34)	2.46 (0.59-10.3)	Insufficient data	1.47 (0.42-5.13)
Increased ORT dose	No (n=46)	1.00	1.00	1.00
	Yes (n=84)	1.62 (0.62-4.23)	0.64 (0.12-3.46)	1.26 (0.55-2.88)
Increased total opioid dose	No (n=46)	1.00	1.00	1.00
	Yes (n=84)	2.06 (0.78-5.43)	0.92 (0.19-4.54)	1.64 (0.72-3.75)
		Initiation of nonmedical benzodiazepine use (n=100)		
Increased opioid analgesic dose	No (n=9)	1.00	1.00	1.00
	Yes (n=22)	0.64 (0.10-4.09)	Insufficient data	1.14 (0.22-5.87)
Increased ORT dose	No (n=35)	1.00	1.00	1.00
	Yes (n=65)	1.21 (0.39-3.74)	0.85 (0.07-10.3)	1.08 (0.40-2.89)
Increased total opioid dose	No (n=35)	1.00	1.00	1.00
	Yes (n=65)			
		Continued nonmedical benzodiazepine use (n=148)		
Increased opioid analgesic dose	No (n=13)	1.00	1.00	1.00
	Yes (n=44)	1.00 (0.25-4.06)	Insufficient data	1.29 (0.34-4.85)
Increased ORT dose	No (n=32)	1.00	1.00	1.00
	Yes (n=116)	2.18 (0.80-5.88)	2.55 (0.50-13.0)	2.30 (0.99-5.35)
Increased total opioid dose	No (n=32)	1.00	1.00	1.00
	Yes (n=116)			
		Initiation of illicit cannabinoid use (n=102)		
Increased opioid analgesic dose	No (n=4)	1.00	1.00	1.00
	Yes (n=18)	Insufficient data	Insufficient data	Insufficient data
Increased ORT dose	No (n=25)	1.00	1.00	1.00
	Yes (n=77)	2.00 (0.10-41.0)	0.42 (0.09-2.04)	0.52 (0.14-1.96)
Increased total opioid dose	No (n=25)	1.00	1.00	1.00
	Yes (n=77)			
		Continued illicit cannabinoid use (n=105)		
Increased opioid analgesic dose	No (n=12)	1.00	1.00	1.00
	Yes (n=32)	0.61 (0.14-2.64)	Insufficient data	0.67 (0.16-2.82)
Increased ORT dose	No (n=23)	1.00	1.00	1.00
	Yes (n=82)	3.51 (1.16-10.6)	2.75 (0.14-55.2)	3.12 (1.13-8.62)
Increased total opioid dose	No (n=23)	1.00	1.00	1.00
	Yes (n=82)	3.20 (1.07-9.60)	2.75 (0.14-55.2)	2.87 (1.05-7.86)

Note: Binary predictor variables were established based on whether or not opioid dose increased during the follow-up period.

Increased opioid dose was significantly associated with continuation of opioid, benzodiazepine and cannabinoid use during the follow-up period, in the comorbid pain group only, but not with initiation of any illicit substance use. Increased ORT dose and total therapeutic opioid dose were shown to be significantly protective of continuation of illicit opioid use, meaning that increased dose was associated with a more than three-fold likelihood of ceasing illicit opioid use during the follow-up period. Conversely, increased therapeutic opioid dose was significantly predictive of continuation of illicit benzodiazepine and cannabinoid use in this group, both associated with a three-fold increase in risk of continuation of illicit use.

3.4.3 Physical morbidity during the 5-year follow-up period

This section begins by reviewing prescribing characteristics indicative of clinically significant physical morbidity (3.5.3.1). The second part of this section (3.5.3.2) considers severe physical morbidity as indicated by inpatient hospital treatment.

3.4.3.1 Prescribing characteristics indicative of clinically significant physical morbidity during the 5-year follow-up period

The proportion of each group in receipt of relevant prescriptions at any point during the 5-year follow-up period is shown in ***Table 3.18***. Beta blockers were included in treatments for cardiovascular disease, in accordance with BNF guidelines; however, this medication is also included in the table indicating psychiatric morbidity (section 3.6.4.1) since beta blockers are also commonly used in the treatment of somatoform disorders. Similarly, anticonvulsants were included in both tables since these medications are commonly used in the treatment of bipolar disorder as well as epilepsy and neuropathic pain. The figures following the table show how prescribing characteristics changed over the 5-year follow-up period.

Table 3.18: *Evidence of clinically significant physical morbidity, based on prescribing data, at any point during the observation period (2005-2010, inclusive)*

Categorical variables	CP		NoP	
	N	%	N	%
Opioid analgesics	***$\chi^2(1)=8.176$; p=0.003 (ω=0.132)***			
Yes	75	31	42	19
No	171	69	179	81
Non-opioid analgesics	***$\chi^2(1)=0.022$; p=0.480 (ω=0.007)***			
Yes	163	66	145	66
No	83	34	76	34
NeuP (amitriptyline & gabapentin)	***$\chi^2(1)=7.502$; p=0.004 (ω=0.127)***			
Yes	75	31	43	20
No	171	69	178	80
Musculoskeletal disease	***$\chi^2(1)=0.798$; p=0.215 (ω=0.041)***			
Yes	187	76	160	72
No	59	24	61	28
Chronic bowel disorders	***$\chi^2(1)=5.751$; p=0.011 (ω=0.111)***			
Yes	102	42	68	31
No	144	58	153	69
Cardiovascular disease	***$\chi^2(1)=0.333$; p=0.319 (ω=0.027)***			
Yes	67	27	55	25
No	179	73	166	75
Anticonvulsants	***$\chi^2(1)=7.936$; p=0.005 (ω=0.130)***			
Yes	64	26	34	15
No	182	74	187	85
Undernourishment	***$\chi^2(1)=0.026$; p=0.482 (ω=0.008)***			
Yes	46	19	40	18
No	200	81	181	82

The following figures show how prescribing characteristics have changed during the 5-year follow-up period. To facilitate repeated measures analyses, participants were included in each of the second graphs if they received relevant prescribed medication at any point during the observation period. The condition intended to treat was provided as a variable in the PIS prescribing dataset, indicated using British National Formulary (BNF) codes.

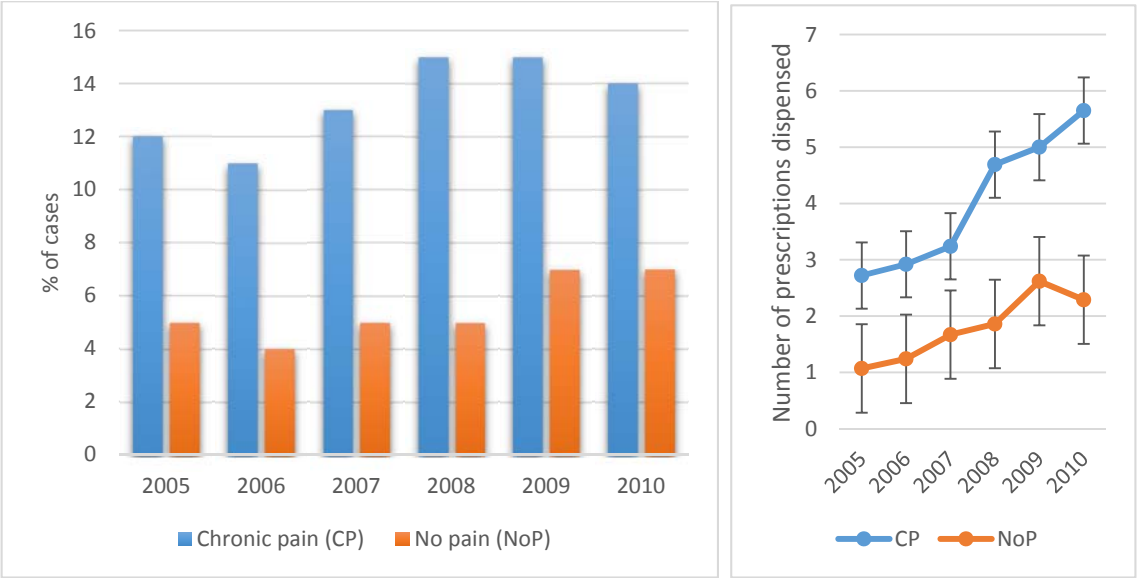


Figure 3.3: *Percentage of the cohort (N=467) prescribed opioid analgesics and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

Chi-square analysis showed that a significantly higher proportion of the CP group was in receipt of prescribed opioid analgesics at study inception ($\chi^2(1)=6.510$; p=0.008; ω=0.118) and at 5-year follow-up ($\chi^2(1)=5.843$; p=0.011; ω=0.112). A repeated-measures analysis of variance of number of prescriptions showed a significant main effect of group (F(1)=5.252; p=0.024; $\eta_p^2=0.044$). The CP group was in receipt of a higher mean number of prescribed opioid analgesics per person during the observation period (4.08, as compared with 1.79 in the NoP group). There was a significant main effect of time with mean number of prescriptions per person increasing during the observation period; however, sphericity was violated (p<0.001; ε=0.436). A Greenhouse-Geisser correction was applied and the effect was no longer significant. There was no significant interaction effect.

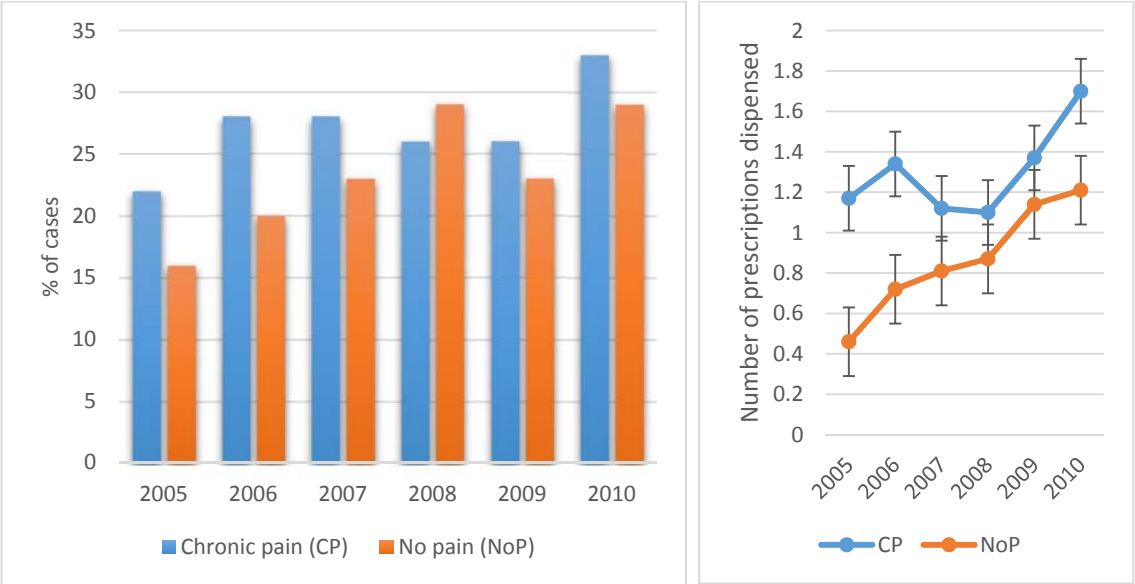


Figure 3.4: *Percentage of the cohort (N=467) prescribed non-opioid analgesics and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

A slightly higher proportion of the CP group was in receipt of prescribed non-opioid analgesics during most of the years in the observation period, however, there was no significant group difference at study inception or at 5-year follow-up. Whilst the CP was in receipt of a relatively higher number of prescriptions per person during the first three years of the observation period, repeated measures analysis of variance revealed that there was no overall significant group difference. There was a main effect of time; however, sphericity was violated ($p<0.001$; $\varepsilon=0.698$). A Greenhouse-Geisser correction was applied and the effect remained significant ($F(3.488)=5.121$; $p=0.001$; $\eta_p^2=0.016$). The overall mean number of prescriptions per person increased significantly from 0.82 in 2005 to 1.46 in 2010. Pairwise comparisons revealed a significant difference between study inception and 5-year follow-up only (+0.64; $p=0.003$). There was no significant interaction effect.

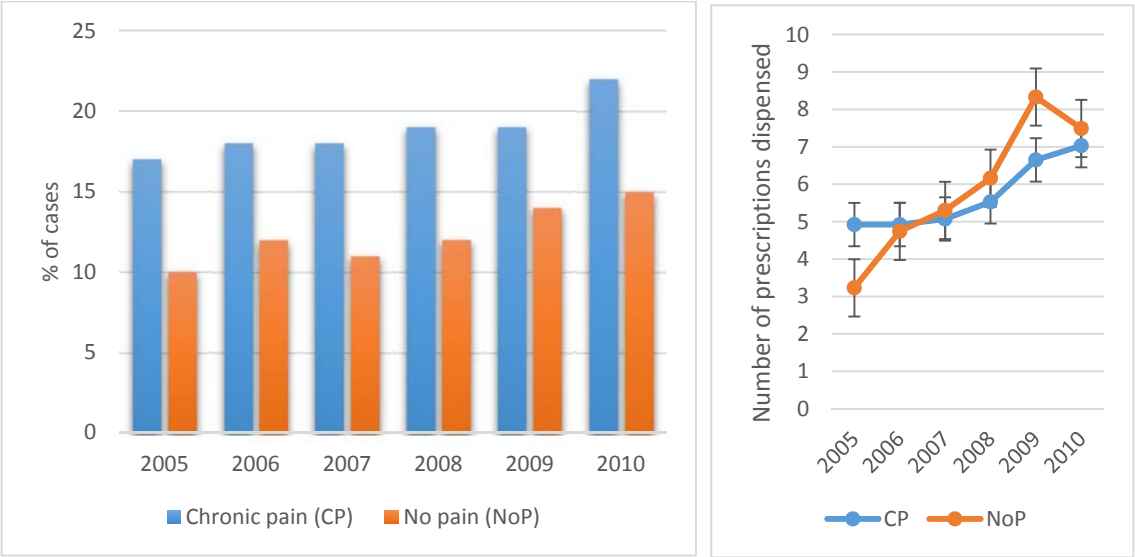


Figure 3.5: *Percentage of the cohort (N=467) prescribed amitriptyline and/or gabapentin, indicative of treatment of neuropathic pain, and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

A greater proportion of the CP group was in receipt of treatment for neuropathic pain; there was no significant group difference at study inception but a significantly higher proportion of the CP group was in receipt of prescribed medication at follow-up ($\chi^2(1)=4.988$; $p=0.026$; $\omega=0.103$). Whilst the NoP group was in receipt of a relatively higher number of prescriptions per person during most years during the observation period, repeated measures analysis of variance revealed that there was no overall significant group difference. There was a main effect of time; however, sphericity was violated ($p<0.001$; $\varepsilon=0.658$). A Greenhouse-Geisser correction was applied and the effect remained significant ($F(3.288)=8.338$; $p<0.001$; $\eta_p^2=0.067$). The overall mean number of prescriptions per person increased significantly from 4.076 in 2005 to 7.258 in 2010. Pairwise comparison revealed significant differences between 2005 and 2009 (+3.41; $p<0.001$) and between 2005 and 2010 (+3.18; $p=0.001$). There was no significant interaction effect.

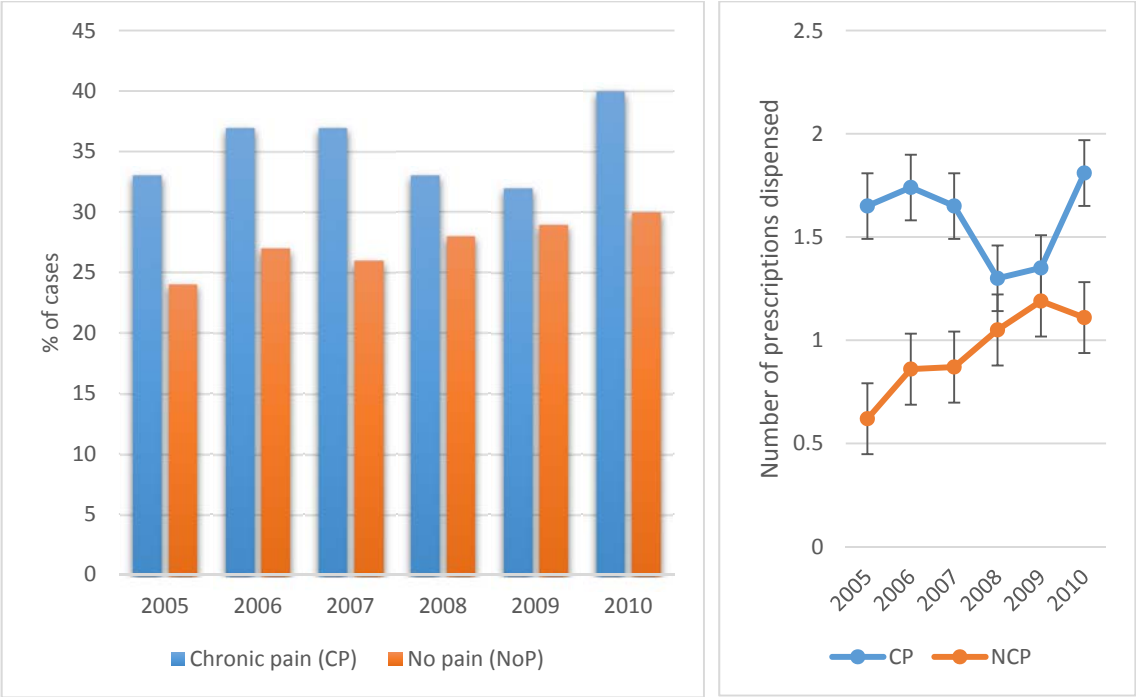


Figure 3.6: *Percentage of the cohort (N=467) prescribed medication for the treatment of musculoskeletal disease and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

A consistently higher proportion of the CP group was in receipt of prescribed medication during the observation period and chi-square analysis showed that a significantly higher proportion of the CP group was in receipt of prescribed medication for the treatment of musculoskeletal disease at study inception ($\chi^2(1)=3.720$; p=0.034; ω=0.089) and at 5-year follow-up ($\chi^2(1)=4.085$; p=0.027; ω=0.094). A repeated-measures analysis of variance showed a significant main effect of group (F(1)=7.321; p=0.007; η_p^2=0.021). The CP group was in receipt of a significantly higher mean number of prescribed opioid analgesics per person during the observation period (1.59, as compared with 0.95 in the NoP group). There was no main effect of time. There was a significant interaction effect; however, sphericity was violated (p<0.001; ε=0.552). A Greenhouse-Geisser correction was applied and the effect was no longer significant.

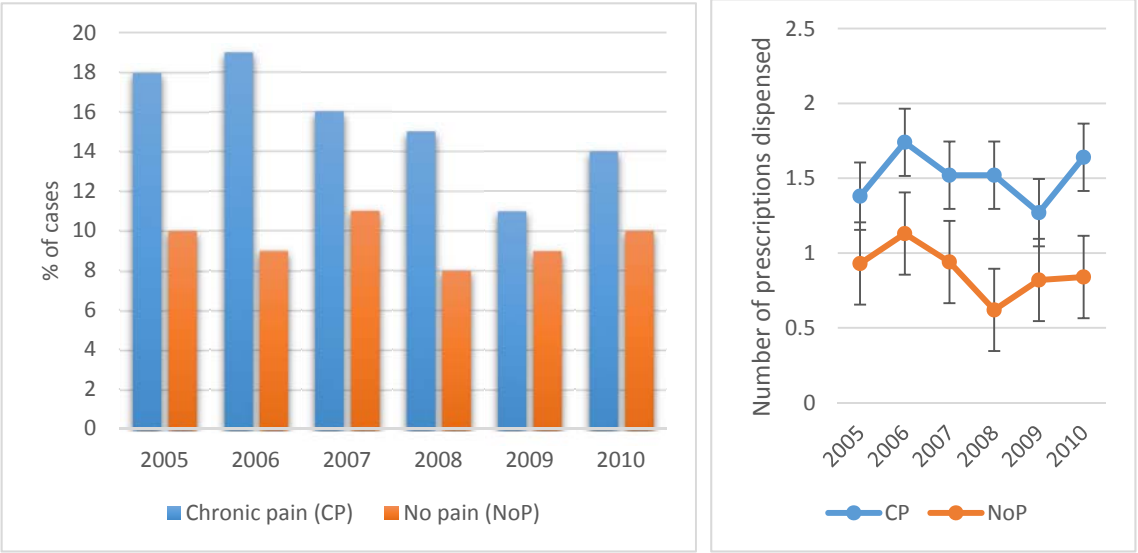


Figure 3.7: *Percentage of the cohort (N=467) prescribed medication for the treatment of chronic bowel disorders and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

A significantly higher proportion of the CP group was in receipt of prescribed medication for the treatment of chronic bowel disorders at inception ($\chi^2(1)=6.035$; $p=0.010$; $\omega=0.114$); however, there was no group difference at 5-year follow-up. Whilst the CP group was in receipt of a consistently higher number of prescriptions per person during the observation period, repeated measures analysis of variance showed no significant group. There was no main effect of time and no interaction effect.

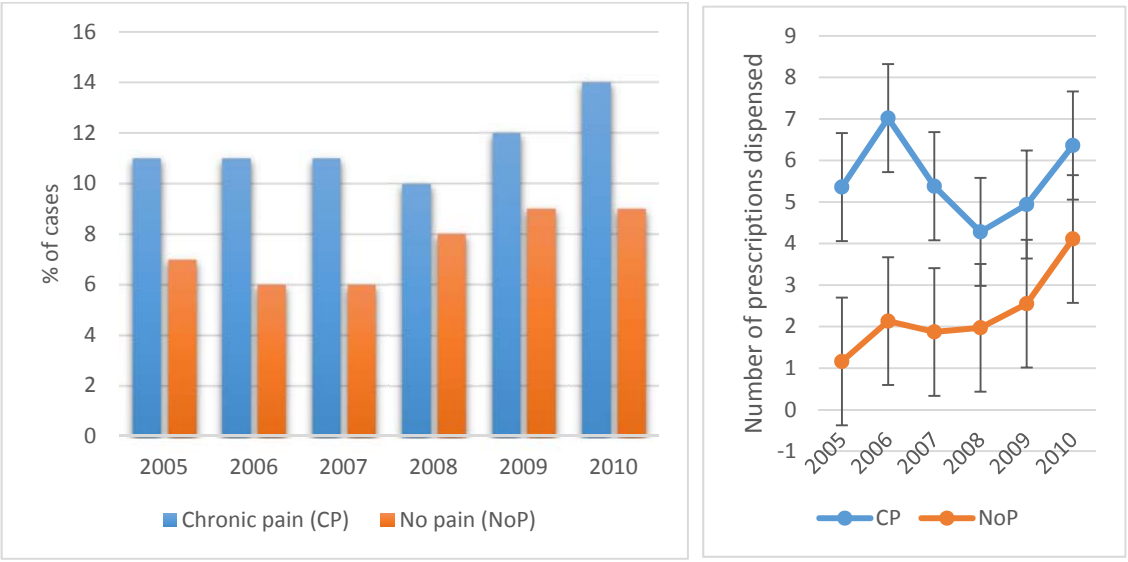


Figure 3.8: *Percentage of the cohort (N=467) prescribed medication for the treatment of cardiovascular disease and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

Although a relatively higher proportion of the CP group was in receipt of prescribed medication for the treatment of cardiovascular disease consistently during each year in the observation period, there was no significant group difference at study inception or at 5-year follow-up.

Whilst the CP group was in receipt of a consistently higher number of prescriptions per person for the treatment of cardiovascular disease in each of the years during the observation period, repeated measures analysis of variance showed no overall significant group difference. There was no main effect of time and no significant interaction effect.

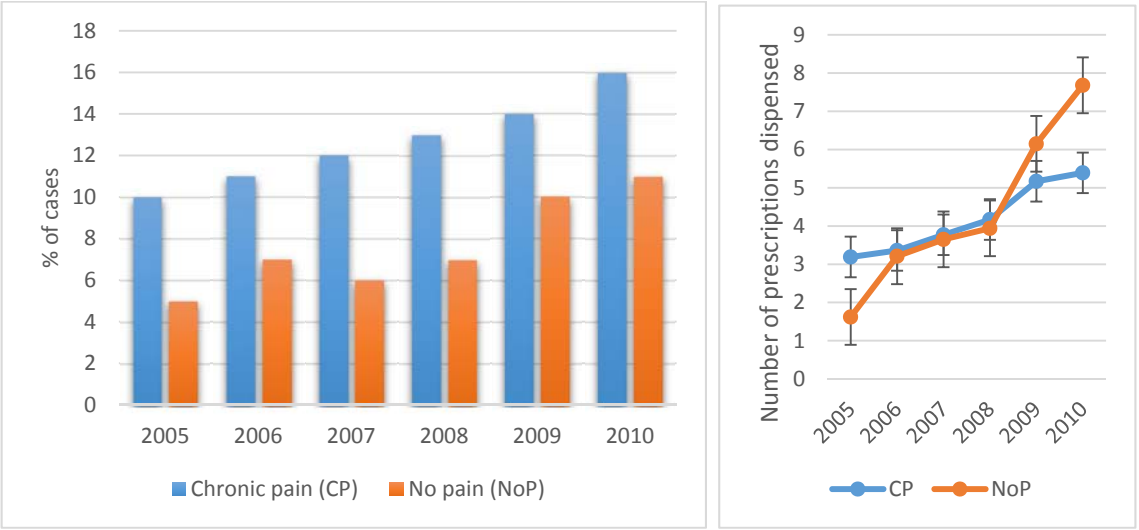


Figure 3.9: *Percentage of the cohort (N=467) prescribed medication for the treatment of epilepsy (however, it should be noted that anticonvulsants are also used in the treatment of bipolar disorder and neuropathic pain) and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

A univariate analysis of variance showed that a significantly higher proportion of the CP group was in receipt of prescribed anticonvulsant medication at inception ($\chi^2(1)=5.337$; $p=0.015$; $\omega=0.107$); however, there was no significant group difference at 5-year follow-up. There was no overall effect of time between inception and follow-up. A repeated-measures analysis of variance showed no significant main effect of group. There was a significant main effect of time; however, sphericity was violated ($p<0.001$; $\varepsilon=0.634$). A Greenhouse-Geisser correction was applied and the effect remained significant ($F(3.168)=9.969$; $p<0.001$; $\eta_p^2=0.094$). The overall mean number of prescriptions per person increased from 2.40 in 2005 to 6.53 in 2010. Pairwise comparisons revealed significant differences between 2005 and 2009 (+3.26; $p=0.002$) and between 2005 and 2010 (+4.13; $p<0.001$). There was no significant interaction effect.

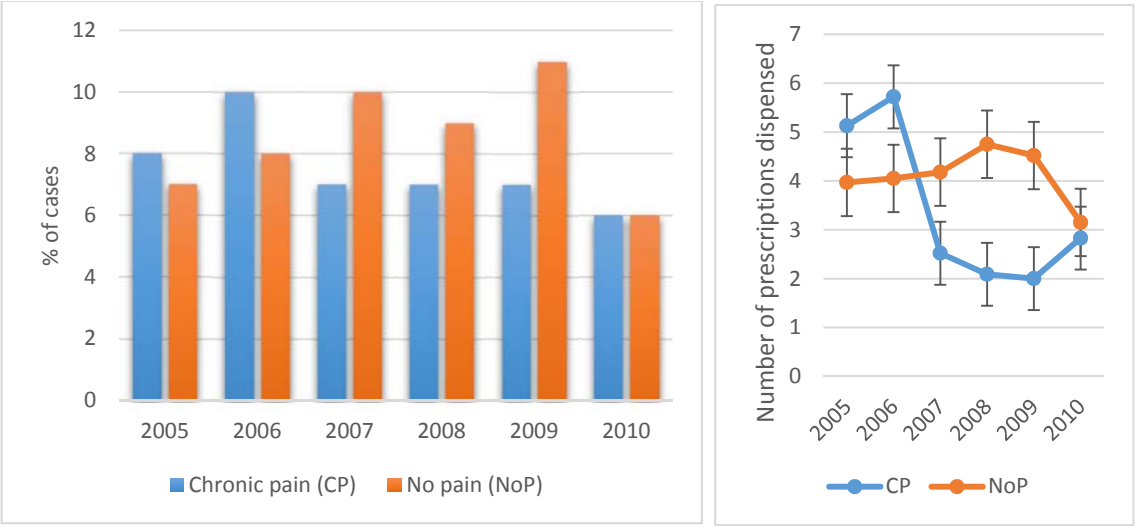


Figure 3.10: *Percentage of the cohort (N=467) prescribed medication for the treatment of undernourishment and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

Chi-square analysis showed no significant group differences at either inception or at 5-year follow-up and no overall effect of time between inception and follow-up. Multivariate analysis of variance showed no significant group effect, no significant main effect of time and no interaction effect.

3.4.3.2 Severe physical morbidity indicated by inpatient treatment during the 5-year follow-up period

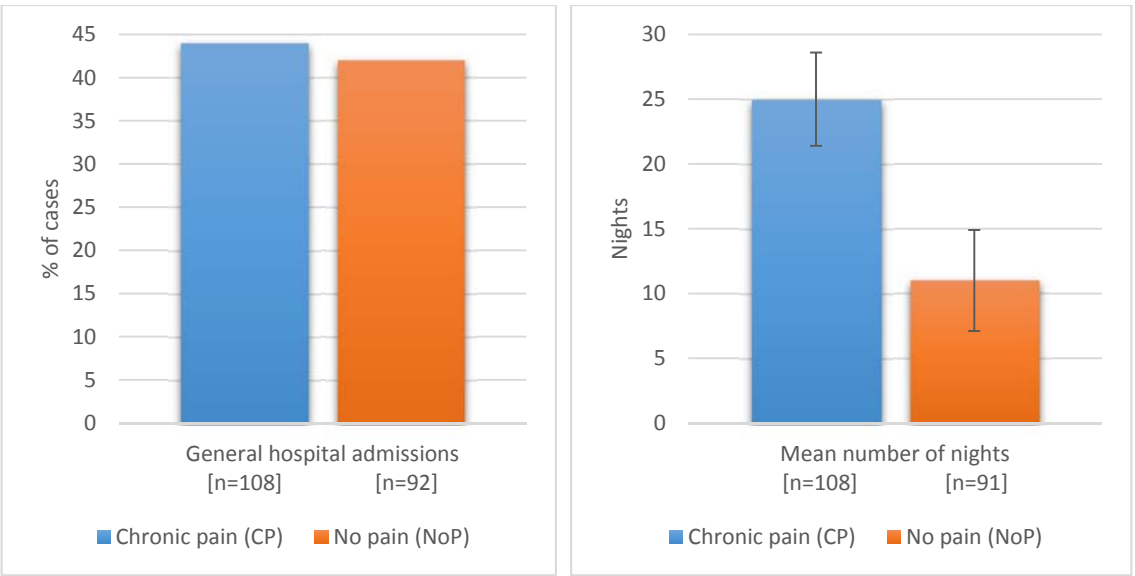


Figure 3.11: *Percentage of the cohort (N=467) admitted to general hospital and the mean number of nights spent in hospital during the 5-year follow-up period. Error bars indicate standard error.*

Just under half of both groups had been admitted to general hospitals on at least one occasion during the observation period; there was no significant effect of group. Mean number of admissions was slightly higher in the CP group (3.13) compared with the NoP group (2.71); however, there was no significant effect of group. The CP group spent significantly more nights in hospital during the observation period (F(1,198)=6.824; p=0.010; η_p^2=0.033); a mean of 25 nights (SD=49; range: 1-373), compared with 11 nights (SD=15; range: 1-105) in the NoP group. Pairwise comparisons revealed a mean difference of -14 nights.

Specific specialties known to be associated with prevalent conditions in ORT populations were examined further; however, due to small number admitted to most specialties, findings are reported in ***Figure 3.12*** solely for the general medicine specialty.

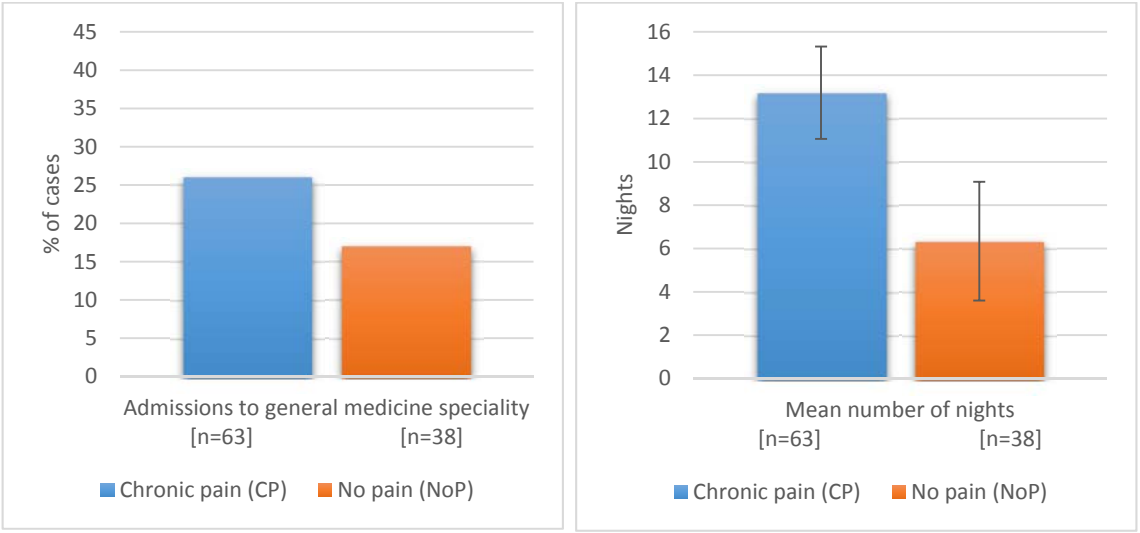


Figure 3.12: *Percentage of the cohort (N=467) admitted to the general medicine speciality and the mean number of inpatient nights in that speciality during the 5-year follow-up period. Error bars indicate standard error.*

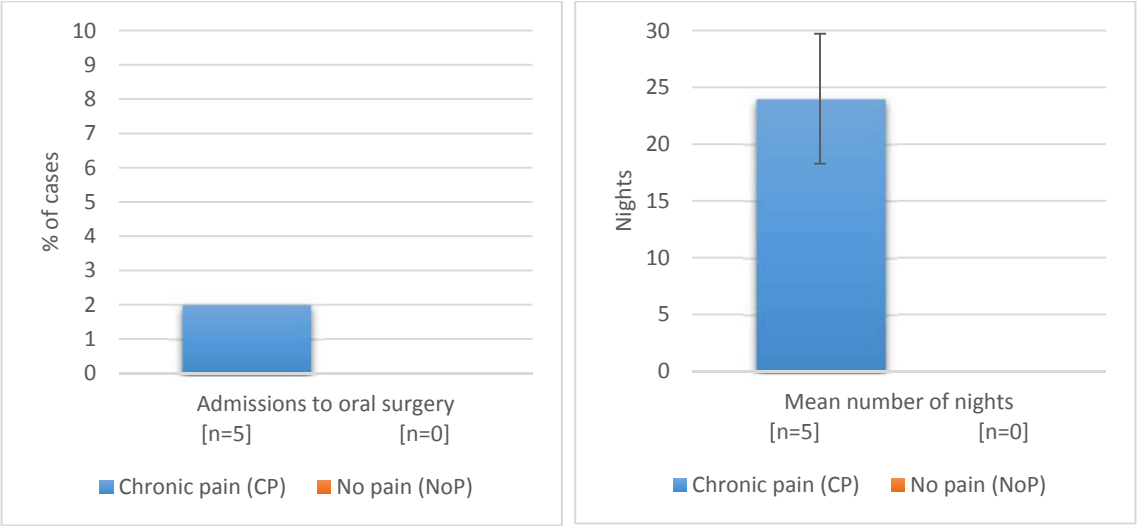


Figure 3.13: *Percentage of the cohort (N=467) admitted to the oral surgery speciality and the mean number of nights spent in that speciality during the 5-year follow-up period. Error bars indicate standard error.*

A significantly higher proportion of the CP group (26% as compared with 17% in the NoP group) was admitted to the general medicine speciality during the observation period ($\chi^2(1)=4.864$; p=0.018; ω=0.102). Cases from the CP group spent significantly more nights in this speciality during this period (F(1,100)=3.944; p=0.050; η_p^2=0.038); a mean of 13 nights (SD=20; range: 1-104), compared with 6 nights (SD=9; range: 1-48) in the NoP group.

Two cases from each group were admitted to the cardiology speciality during the observation period; therefore, there was no significant effect of group. Cases from the CP group spent more nights in this speciality during this period (a mean of 35 nights (SD=49; range: 1-69), compared with 4 nights (SD=1; range: 3-4) in the NoP group). Perhaps as a consequence of the small number of cases and the range in the CP group, this did not represent a significant effect of group.

Two cases from the CP group and three cases from the NoP group were admitted to the vascular surgery speciality during the observation period; therefore, there was no significant effect of group. There was, however, a significant effect of group concerning number of nights spent within the vascular surgery speciality (F(1,4)=22.722; p=0.018; η_p^2=0.833). Cases from the CP group spent more nights in this speciality during this period (a mean of 41 nights (SD=3; range: 39-43), compared with 14 nights (SD=7; range: 6-19) in the NoP group).

There was a significant effect of group concerning admission to the oral surgery speciality ($\chi^2(1)=4.540$; p=0.040; ω=0.099); a significantly higher proportion of cases from the CP group (2%, n=5) were admitted to this speciality as compared with no cases in the NoP group. Cases from the CP group spent significantly more nights in this speciality during this period (F(1,4)=16.386; p=0.016; η_p^2=0.804); a mean of 24 nights (SD=13; range: 1-34), compared with no nights in the NoP group (***Figure 3.13***).

3.5.4 Psychiatric morbidity during the 5-year follow-up period

This section begins by reviewing prescribing characteristics indicative of clinically significant psychiatric morbidity (3.5.4.1). Two prescription items from this section are also contained in the corresponding section addressing physical morbidity (3.5.3.1): beta blockers are commonly used to treat cardiovascular disease and somatic symptoms in anxiety disorders; and anticonvulsants are commonly used to treat epilepsy/neuropathic pain and manic symptoms in bipolar disorder. The second part of this section (3.5.4.2) considers severe psychiatric morbidity as indicated by inpatient hospital treatment.

3.4.4.1 Prescribing characteristics indicative of clinically significant psychiatric morbidity during the 5-year follow-up period

The proportion of each group in receipt of relevant prescriptions at any point during the 5-year follow-up period is shown in ***Table 3.19***. The figures following the table show how prescribing characteristics changed over the 5-year follow-up period. To facilitate repeated measures analyses, participants were included in each of the second graphs if they received relevant prescribed medication at any point during the observation period

Table 3.19: *Evidence of clinically significant psychiatric morbidity during the observation period (2005-2010, inclusive)*

Categorical variables	CP		NoP	
	N	%	N	%
Anxiolytics	***$\chi^2(1)=3.071$; p=0.049 (ω=0.081)***			
Yes	164	67	130	59
No	82	33	91	41
Beta blockers (somatoform disorders)	***$\chi^2(1)=0.000$; p=0.553 (ω=0.000)***			
Yes	30	12	27	12
No	216	88	194	88
Mood disorders	***$\chi^2(1)=1.562$; p=0.126 (ω=0.058)***			
Yes	181	74	151	68
No	65	26	70	32
Anticonvulsants (bipolar mood disorders)	***$\chi^2(1)=7.936$; p=0.005 (ω=0.130)***			
Yes	64	26	34	15
No	182	74	187	85
Insomnia	***$\chi^2(1)=0.842$; p=0.205 (ω=0.042)***			
Yes	90	37	90	41
No	156	63	131	59
Antipsychotics	***$\chi^2(1)=0.002$; p=0.529 (ω=0.002)***			
Yes	43	18	39	18
No	203	82	182	82

All participants, when in treatment, were in receipt of methadone maintenance therapy.

Figure 3.14 shows the mean and maximum prescribed daily doses of methadone treatment.

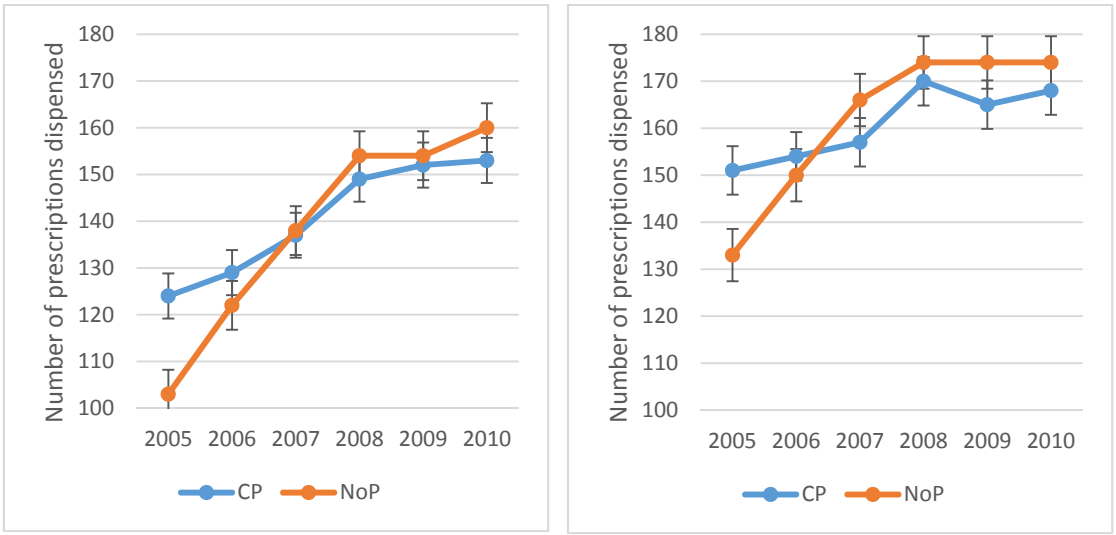


Figure 3.14: *Mean and maximum prescribed daily dose of methadone in the cohort (N=467) during the 5-year follow-up period. Error bars indicate standard error.*

A repeated-measures analysis of variance showed no significant main effect of group concerning mean prescribed daily dose of methadone. A Greenhouse-Geisser correction determined a significant effect of time (F(2.79,630.04)=21.405; p<0.001; η_p^2=0.087). *Post hoc* tests, using Bonferroni correction, revealed that there were significant differences between each of the first three years in the observation period and all other time points but that there were no differences between the final three years. Pairwise comparisons are shown in ***Table 3.20***. There was a significant main interaction effect of group and time (F(2.78,628.61)=4.356; p=0.006; η_p^2 =0.019). Analysis of simple main effects revealed a significant group difference at inception (F(1,227)=7.822; p=0.006; η_p^2=0.033) with the CP group in receipt of a significantly higher mean daily dose than the NoP group (mean difference = 21mg) but no significant group differences at any other time points.

The maximum diazepam-equivalent daily dose was identified for each patient in each year and the group mean of the individual values was computed. A repeated-measures analysis of variance showed no significant main effect of group concerning maximum prescribed daily dose of methadone. A Greenhouse-Geisser correction determined a main effect of time (F(2.79,630.04)=3.851; p=0.011; η_p^2=0.017). *Post hoc* tests, using Bonferroni correction, revealed that there were significant differences between each of the first three years in the observation period but that there were no differences between the final three years. There was a significant main interaction effect of group and time (F(2.80,629.14)=3.649; p=0.015; η_p^2 =0.016). Analysis of simple main effects revealed a significant group difference at inception (F(1,227)=4.695; p=0.032; η_p^2=0.020) with the CP group in receipt of a significantly higher mean daily dose than the NoP group (mean difference = 18mg) but no significant group differences at any other time points.

Table 3.20: *Pairwise comparisons of the effect of time on mean and maximum prescribed daily dose of methadone*

Mean prescribed daily dose of methadone				**Maximum prescribed daily dose of methadone**			
Time (I)	**Time (J)**	**Mean diff. (I-J)**	***p***	**Time (I)**	**Time (J)**	**Mean diff. (I-J)**	***p***
2005	2006	-12.029	<0.001	2005	2006	-9.877	0.031
	2007	-23.857	<0.001		2007	-19.258	<0.001
	2008	-37.922	<0.001		2008	-30.250	<0.001
	2009	-39.742	<0.001		2009	-27.465	<0.001
	2010	-42.799	<0.001		2010	-28.828	<0.001
2006	2007	-11.828	<0.001	2006	2007	-9.381	0.074
	2008	-25.893	<0.001		2008	-20.373	<0.001
	2009	-27.712	<0.001		2009	-17.588	<0.001
	2010	-30.770	<0.001		2010	-18.951	<0.001
2007	2008	-14.065	<0.001	2007	2008	-10.991	0.002
	2009	-15.884	<0.001		2009	-8.206	0.175
	2010	-18.942	<0.001		2010	-9.570	0.146
2008	2009	-1.819	1.000	2008	2009	+2.785	1.000
	2010	-4.877	1.000		2010	+1.422	1.000
2009	2010	-3.057	1.000	2009	2010	-1.363	1.000

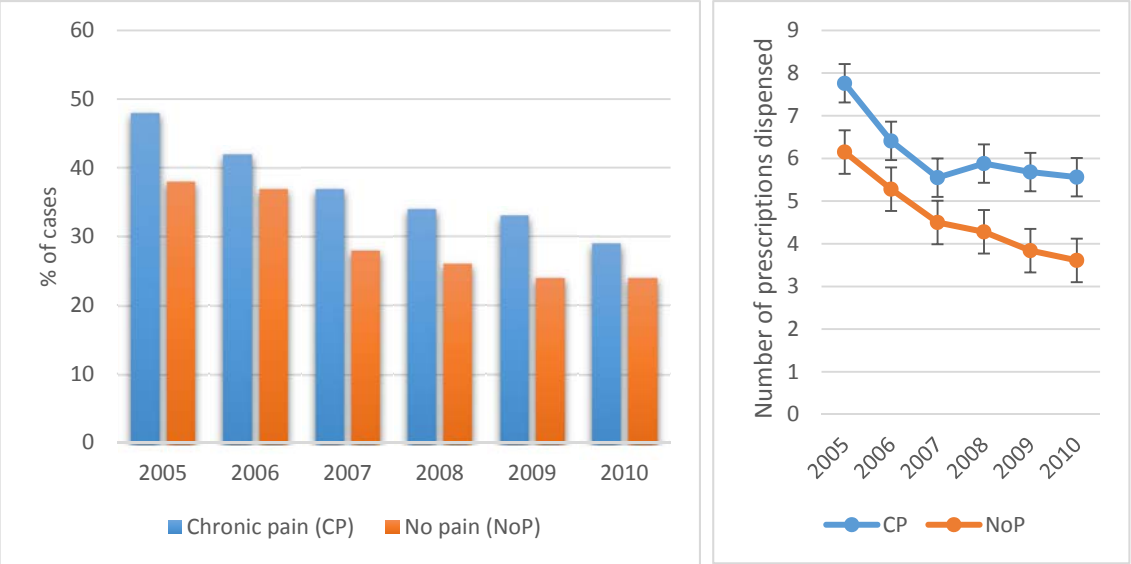


Figure 3.15: *Percentage of the cohort (N=467) prescribed medication for the treatment of anxiety disorders and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

A significantly higher proportion of the CP group was in receipt of prescribed medication for the treatment of anxiety disorders at inception ($\chi^2(1)=5.090$; p=0.015; ω=0.104); however, there was no group difference at 5-year follow-up and there was no overall effect of time between inception and follow-up.

The CP group was in receipt of a significantly higher overall mean number of prescriptions per person for the treatment of anxiety disorders (F(1)=5.059; p=0.025; η_p^2=0.017); pairwise comparison determined a mean difference of -1.53. There was a main effect of time; however, sphericity was violated (p<0.001; ε=0.673). A Greenhouse-Geisser correction was applied and the effect remained significant (F(3.364)=8.245; p<0.001; η_p^2=0.028). The mean number of prescriptions decreased over time and pairwise comparison determined a significant difference between 2005 and 2007 (-1.93; p=0.001), between 2005 and 2008 (-1.88; p=0.002), between 2005 and 2009 (-2.20; p<0.001) and between 2005 and 2010 (-2.37; p<0.001). There were no other differences on pairwise comparison. There was no significant interaction effect.

Many participants were treated with anxiolytics intermittently during the observation period and, in consequence, the absence of treatment for one or more years often did not indicate complete cessation of treatment. To enable examination of the interaction effect in the entire population, rather than simply the very small proportion that was in receipt of prescribed benzodiazepine during the entire observation period (n=61, 12% of the entire population), those that had received benzodiazepine treatment at any point during the observation period were coded with a zero for years during which they received no anxiolytic medication. Findings are reported in ***Figure 3.16***.

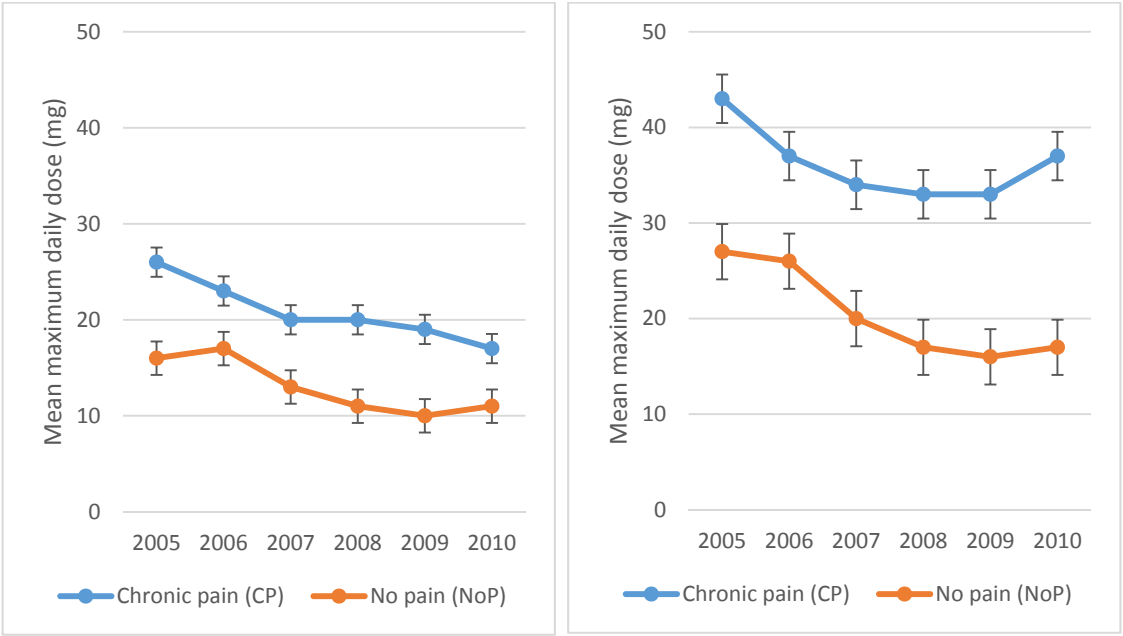


Figure 3.16: *Mean and maximum prescribed daily dose of benzodiazepine medication (diazepam-equivalent dose in mg) in the cohort (N=467) during the 5-year follow-up period. Error bars indicate standard error.*

Repeated measures analysis of variance of mean daily benzodiazepine-equivalent dose showed an overall group effect (F(1,294)=10.887; p=0.001; η_p^2=0.036). The CP group was in receipt of an overall higher dose during the observation period and pairwise comparison revealed a mean difference of +7.63mg. There was a main effect of time; however, sphericity was violated (p<0.001; ε=0.695). A Greenhouse-Geisser correction was applied and the effect remained significant (F(3.476)=6.949; p<0.001; η_p^2=0.023). The mean dose decreased over time and pairwise comparison determined a significant difference between 2005 and 2008 (-5.24mg; p=0.024), 2009 (-6.26; p=0.003) and 2010 (-6.98; p=0.003) and between 2006 and 2008 (-4.18; p=0.044), 2009 (-5.20; p=0.016) and 2010 (-5.92; p=0.020). There was no significant interaction effect.

The maximum diazepam-equivalent daily dose was identified for each patient in each year and the group mean of the individual values was computed. Repeated measures analysis of variance of maximum daily benzodiazepine-equivalent dose showed an overall group effect (F(1,294)=14.718; p<0.001; η_p^2=0.048). The CP group was in receipt of an overall higher dose during the observation period and pairwise comparison revealed a mean difference of +14.75mg. There was a main effect of time; however, sphericity was violated (p<0.001; ε=0.759). A Huynh-Feidt correction was applied and the effect remained significant (F(3.863)=5.66; p<0.001; η_p^2=0.019). The mean dose decreased over time and pairwise comparison determined a significant difference between 2005 and 2007 (-7.77mg; p=0.034), 2008 (-9.17mg; p=0.014), 2009 (-9.88; p=0.009) and 2010 (-11.12; p=0.006). There was no significant interaction effect.

Whilst the analyses reported in ***Figure 3.16*** permitted an exploration of the effect of time and interaction effects, absolute mean dose was 'diluted' since all individuals that were in receipt of a benzodiazepine prescription at any point during the observation were included (but scored a zero for each year that no prescriptions were received). In order to establish an accurate mean dose for each year, and to enable group comparisons based on the absolute mean dose, univariate analysis of variance was undertaken for each year. These analyses included only individuals who were in receipt of a benzodiazepine prescription during each of these years. Findings are reported in ***Figure 3.17***.

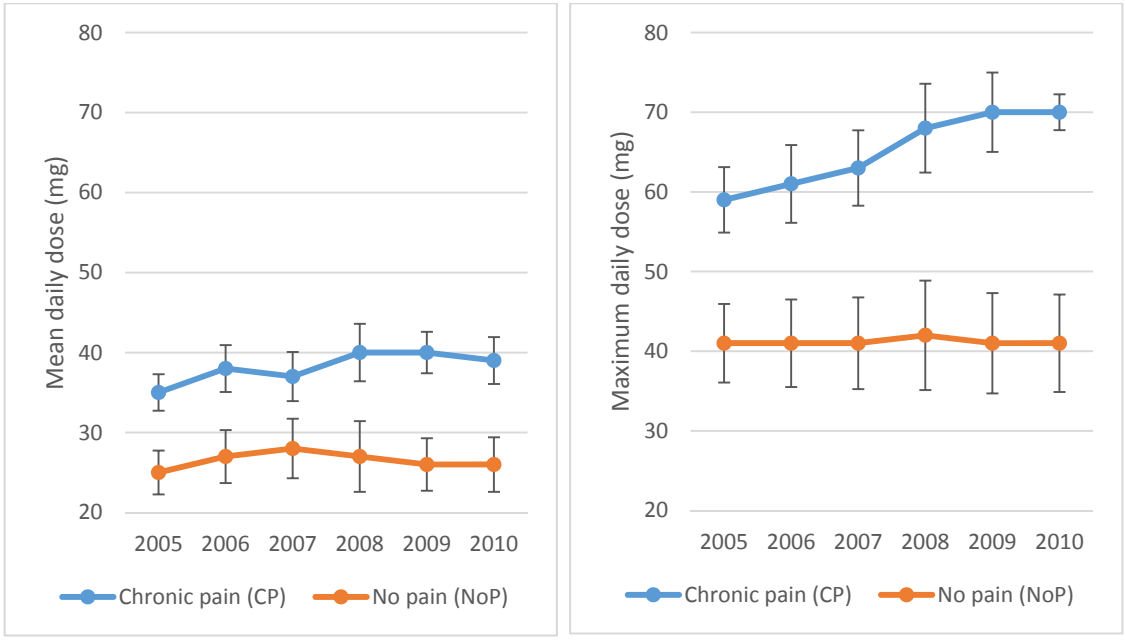


Figure 3.17: *Mean and maximum prescribed daily dose of benzodiazepine medication (diazepam-equivalent dose in mg) in the cohort (N=467) during the 5-year follow-up period. Error bars indicate standard error.*

Univariate analysis of variance of mean diazepam-equivalent daily dose showed a significant group differences in all but one year during the observation period. The CP group reported a higher mean daily dose than the NoP group in 2005 (+10.08mg; p=0.005), 2006 (+11.18mg; p=0.012), 2007 (+9.27mg; p=0.056), 2008 (+12.76mg; p=0.027), 2009 (+13.52; p=0.002) and 2010 (+13.36; p=0.004).

The maximum diazepam-equivalent daily dose was identified for each patient in each year and the group mean of the individual values was computed. Univariate analysis of variance of maximum diazepam-equivalent daily dose showed significant group differences in each of the years during the observation period with the disparity between groups increasing over time. The CP group was associated with a higher maximum daily dose than the NoP group in 2005 (+17.93mg; p=0.006), 2006 (+19.87mg; p=0.007), 2007 (+21.72mg; p=0.004), 2008 (+25.97mg; p=0.004), 2009 (+28.51; p=0.001) and 2010 (+29.39; p<0.001).

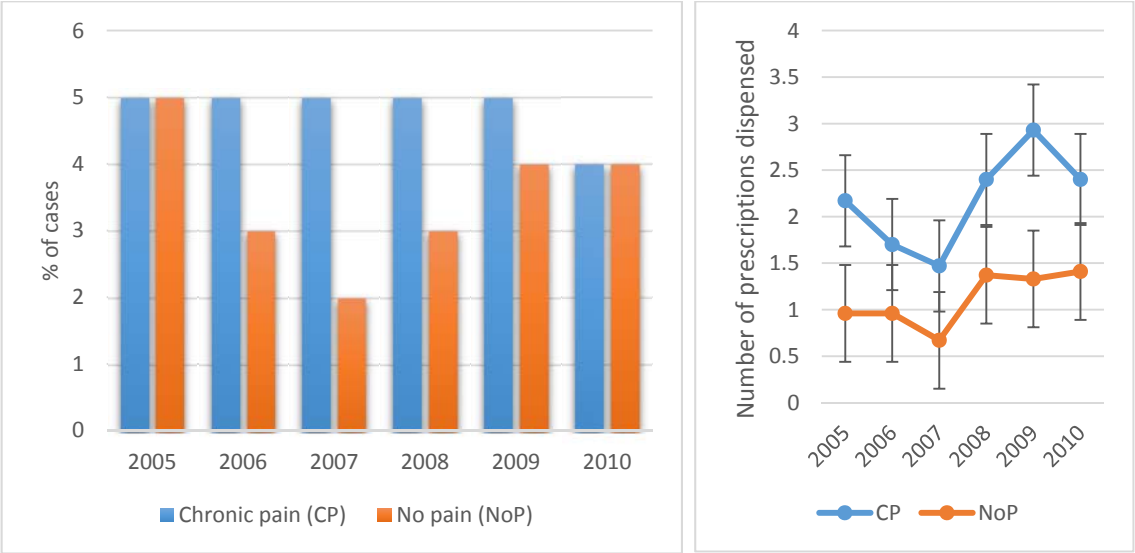


Figure 3.18: *Percentage of the cohort (N=467) prescribed beta blockers for the possible treatment of somatic symptoms in anxiety disorders (however, it should be noted that beta blockers are also used in the treatment of cardiovascular disease) and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

Although a relatively higher proportion of the CP group was in receipt of prescribed beta blockers consistently during the period 2006-2009, inclusive, there was no significant group difference at study inception or at 5-year follow-up. Furthermore, there was no overall effect of time between inception and follow-up.

Whilst the CP group was in receipt of a consistently higher mean number of prescribed beta blockers per person during the observation period, there was no overall significant group difference. There was no overall effect of time and no significant interaction effect.

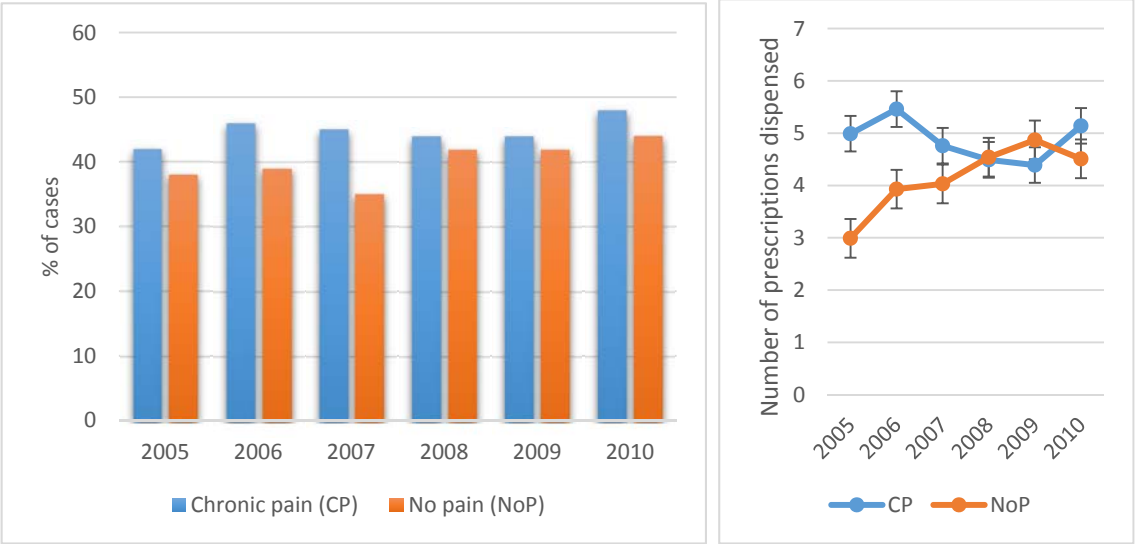


Figure 3.19: *Percentage of the cohort (N=467) prescribed antidepressant medication for the treatment of mood disorders and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

The proportion of each group in receipt of prescribed medication for the treatment of mood disorders was relatively similar; there was no significant group difference at study inception or at 5-year follow-up and no overall effect of time between inception and 5-year follow-up.

Repeated measures analysis of variance of number of prescriptions showed no significant overall effect of group or time concerning mean number of prescriptions per person dispensed for the treatment of mood disorders. There was a significant interaction effect; however, sphericity was violated ($p<0.001$; $\varepsilon=0.593$). A Greenhouse-Geisser correction was applied and the effect remained significant ($F(2.966)=4.228$; $p=0.006$; $\eta_p^2=0.013$). Whilst the mean number of prescriptions remained relatively consistent over time in the CP group (4.99 in 2005 and 5.14 in 2010), there was a steady increase in the number within the NoP group (ranging from 2.99 in 2005 to 4.87 in 2010).

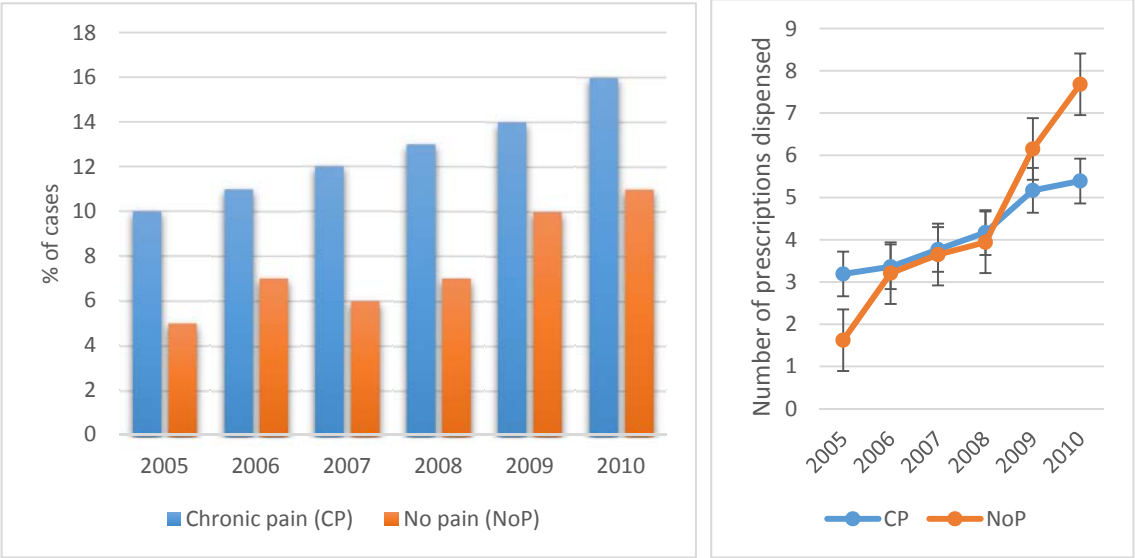


Figure 3.20: *Percentage of the cohort (N=467) prescribed anticonvulsant medication for the possible treatment of bipolar disorder (however, it should be noted that this medication is also used in the treatment of epilepsy and neuropathic pain) and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

A univariate analysis of variance showed that a significantly higher proportion of the CP group was in receipt of prescribed anticonvulsant medication at study inception ($\chi^2(1)=5.337$; p=0.015; ω=0.107); however, there was no significant group difference at 5-year follow-up. There was no overall effect of time between inception and follow-up.

A repeated-measures analysis of variance of number of prescriptions showed no significant main effect of group. There was a significant main effect of time; however, sphericity was violated (p<0.001; ε=0.634). A Greenhouse-Geisser correction was applied and the effect remained significant (F(3.168)=9.969; p<0.001; η_p^2=0.094). Pairwise comparison revealed a significant difference between 2005 and 2009 (+3.26; p=0.002) and between 2005 and 2010 (+4.13; p<0.001). There was no significant interaction effect.

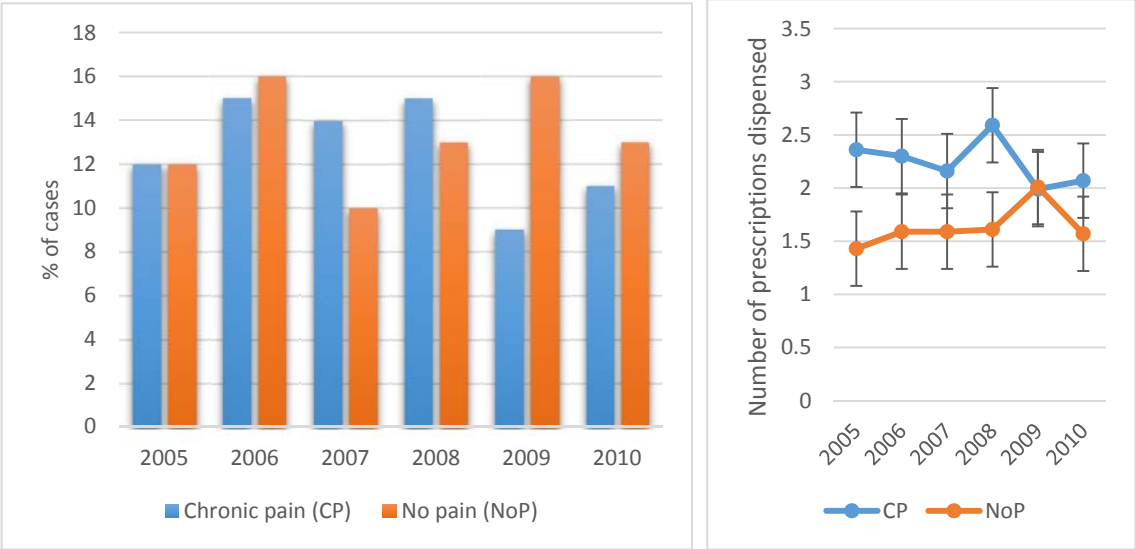


Figure 3.21: *Percentage of the cohort (N=467) prescribed medication for the treatment of insomnia and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

The proportion of each group in receipt of prescribed medication for the treatment of insomnia (hypnotics or barbiturates) was relatively similar; there was no significant group difference at inception or at 5-year follow-up and no overall effect of time between inception and 5-year follow-up.

Whilst the CP group was in receipt of a relatively higher mean number of prescriptions per person for the treatment of insomnia during most years in the observation period, there was no overall significant group difference. There was no overall effect of time and no significant interaction effect.

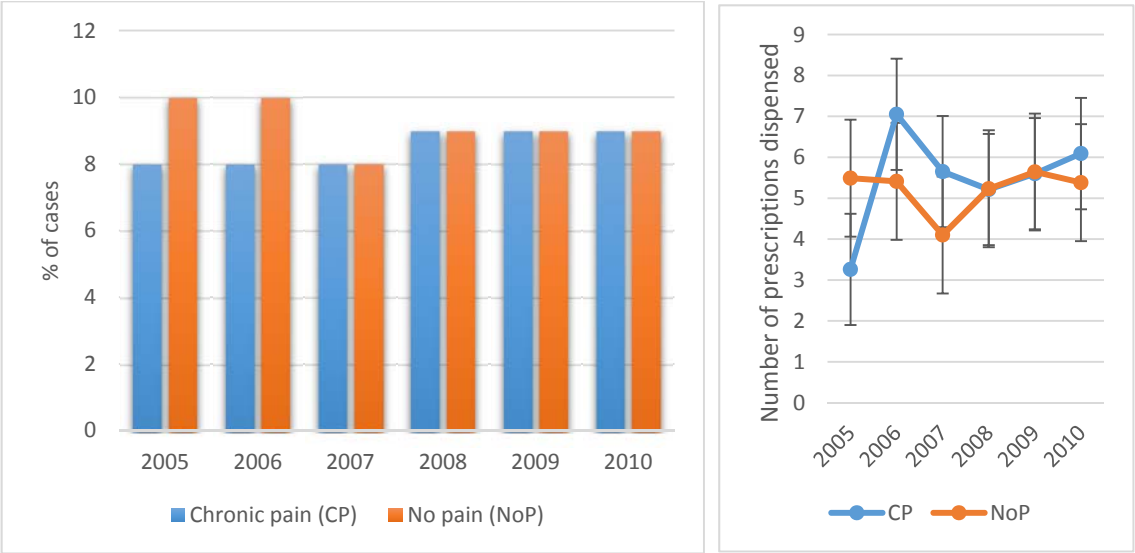


Figure 3.22: *Percentage of the cohort (N=467) prescribed medication for the treatment of psychotic disorders and the mean number of prescriptions dispensed per patient per annum during the 5-year follow-up period. Error bars indicate standard error.*

The proportion of each group in receipt of prescribed medication for the treatment of psychotic disorders was relatively similar; there was no significant group difference at inception or at 5-year follow-up and no overall effect of time between inception and 5-year follow-up.

Both groups were in receipt of a similar mean number of prescriptions per person for the treatment of psychotic disorders during the observation period; there was no overall significant group difference, no overall effect of time and no significant interaction effect.

3.4.4.2 Severe psychiatric morbidity during the 5-year follow-up period

The data concerning number of nights in hospital were normally distributed with the exception of one case from the NoP group who had stayed in hospital for a total number of 1186 nights during the observation period with a longest single stay of 862 nights. In consequence, this outlying case was excluded from analyses to avoid distortion.

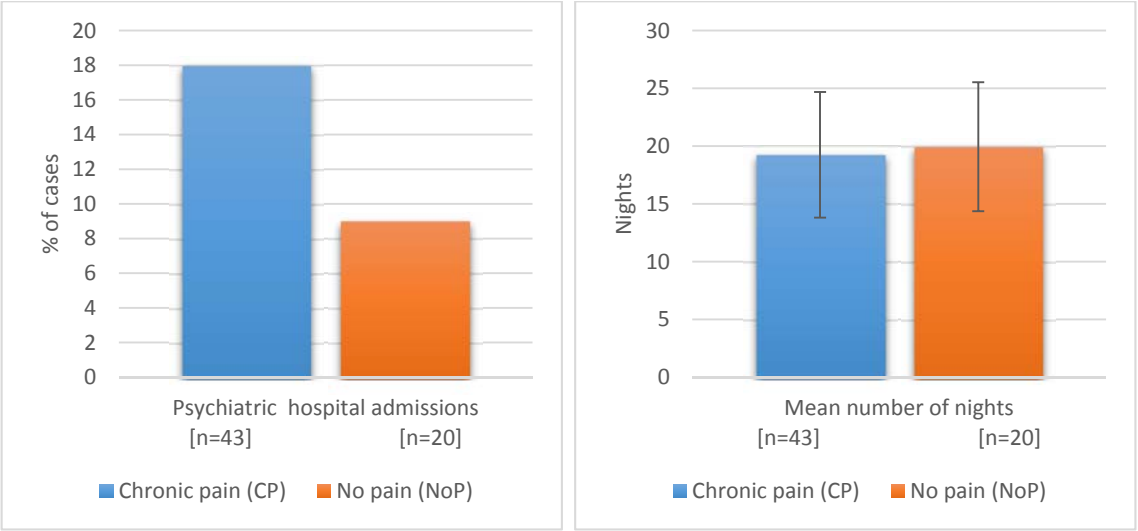


Figure 3.23: *Percentage of the cohort (N=467) admitted to psychiatric hospitals and the mean number of nights spent in hospital during the 5-year follow-up period. Error bars indicate standard error.*

A significantly higher proportion of the CP group (18% compared with 9% of the NoP group) was admitted to psychiatric hospitals during the observation period ($\chi^2(1)=7.089$; $p=0.005$; $\omega=0.123$). Mean number of admissions was slightly lower in the CP group (2.00) compared with the NoP group (2.65); there was no significant effect of group. Mean total number of nights spent in hospital during the observation period was slightly lower in the CP group (19 nights) compared with the NoP group (20 nights); there was no significant effect of group. Longest single stay was slightly higher in the CP group (16 nights) compared with the NoP group (12 nights); there was no significant effect of group.

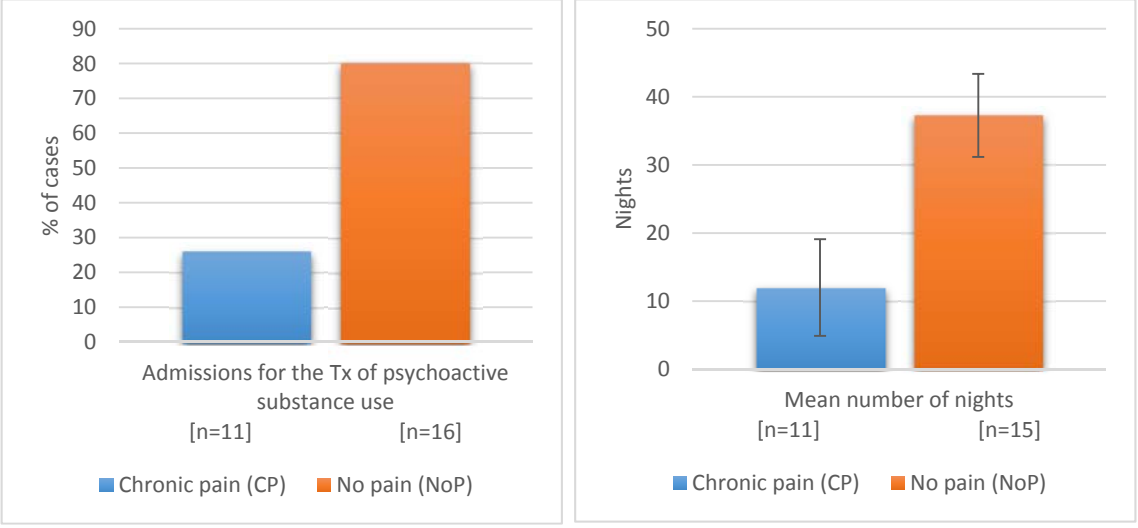


Figure 3.24: *Percentage of the cohort (N=467) admitted for the treatment of psychoactive substance use and the mean number of nights spent in hospital for the treatment of this condition during the 5-year follow-up period. Error bars indicate standard error.*

A significantly lower proportion of the CP group (26% compared with 75% of the NoP group) was admitted to psychiatric hospitals during the observation period for the treatment of psychoactive substance use ($\chi^2(1)=15.957$; $p<0.001$; $\omega=0.507$). Those that were admitted from the CP group spent significantly fewer nights ($F(1,25)=7.306$; $p=0.012$; $\eta_p^2=0.233$) and pairwise comparison demonstrated a mean difference of -25.27 nights.

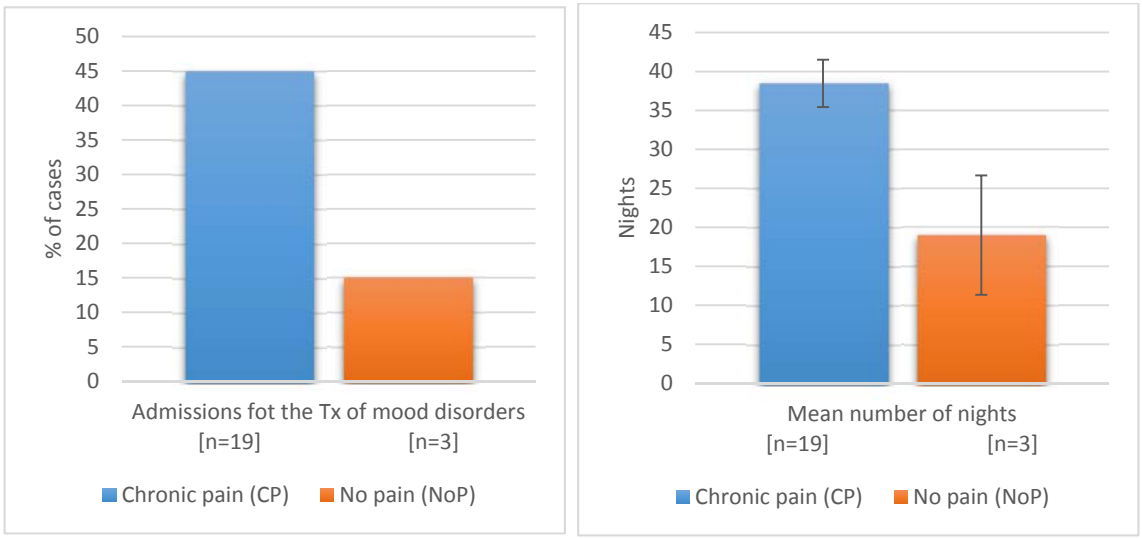


Figure 3.25: *Percentage of the cohort (N=467) admitted for the treatment of mood disorders and the mean number of nights spent in hospital for the treatment of this condition during the 5-year follow-up period. Error bars indicate standard error.*

A significantly higher proportion of the CP group (45% compared with 15% of the NoP group) was admitted to psychiatric hospitals during the observation period for the treatment of mood disorders ($\chi^2(1)=5.411$; $p=0.018$; $\omega=0.295$). Those that were admitted from the CP group spent significantly more nights in hospital ($F(1,21)=5.588$; $p=0.028$; $\eta_p^2=0.218$) and pairwise comparison demonstrated a mean difference of +19.47 nights.

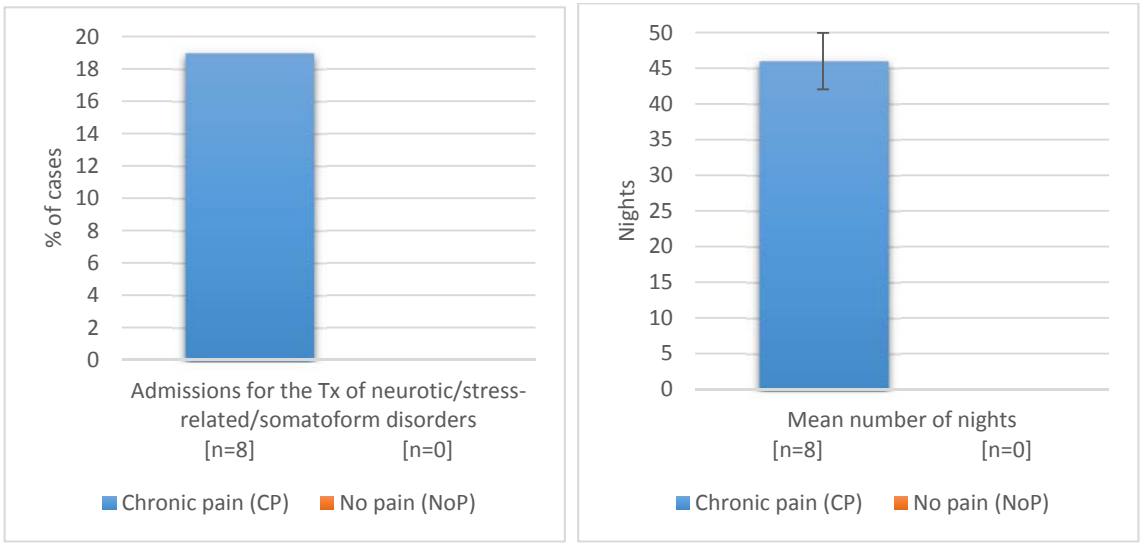


Figure 3.26: *Percentage of the cohort (N=467) admitted for the treatment of neurotic/stress-related/somatoform disorders and the mean number of nights spent in hospital for the treatment of these disorders during the 5-year follow-up period. Error bars indicate standard error.*

A significantly higher proportion of the CP group (19% compared with none of the NoP group) was admitted to psychiatric hospitals during the observation period for the treatment of neurotic, stress-related and somatoform disorders ($\chi^2(1)=4.374$; $p=0.035$; $\omega=0.266$). Those that were admitted from the CP group spent a mean number of 46 nights in hospital; however, due to there being no cases in the NoP group, there were insufficient data for statistical comparison.

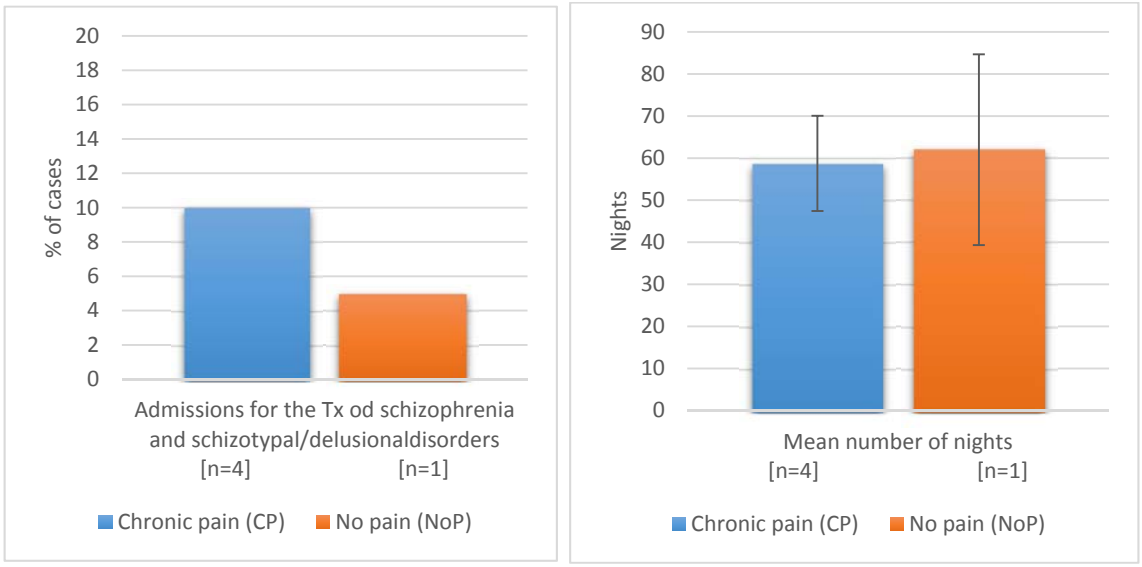


Figure 3.27: *Percentage of the cohort (N=467) admitted for the treatment of psychotic disorders and the mean number of nights spent in hospital for the treatment of these disorders during the 5-year follow-up period. Error bars indicate standard error.*

A slightly higher proportion of the CP group (10% compared with 5% of the NoP group) was admitted to psychiatric hospitals during the observation period for the treatment of schizophrenia and schizotypal and delusional disorders; however, there was no significant effect of group. Cases from the CP group spent a mean number of 59 nights in hospital as compared with 62 nights in the NoP group; there was no significant effect of group.

3.5 Summary of chapter findings

In addressing the first objective, the representativeness of the study cohort was examined. The study cohort (n=521) was shown to be broadly representative of the entire treatment population (n=626) with very few significant differences between those that were included and those that were excluded due to an absence of BPI-SF data.

In addressing the second objective, ORT patients with comorbid chronic pain were compared with ORT patients with no pain. The aim was to determine whether these two groups were similar at study inception or presented as clinically-distinct groups associated with specific treatment challenges. The two groups were very similar concerning demographic and socioeconomic characteristics. Biochemical drug screen results indicated the a significantly higher proportion of the CP group was misusing benzodiazepines and cannabinoids but that there was no group difference concerning illicit opioid use. A significantly higher proportion of the CP group reported physical health problems at study inception and these reports were corroborated by standardised testing using the physical health subscale of the MAP. Additionally, the CP group reported a significantly higher prevalence of mental health problems and these reports were corroborated by standardised testing using both the GHQ-28 and the CORE (an all of their subscales). A significantly higher proportion of the CP group was in receipt of a diazepam prescription at study inception, a significantly higher mean daily diazepam dose and a significantly higher mean daily methadone dose. A lower mean score on the TPQ indicated that the CP group was significantly less satisfied with treatment received in the ORT setting compared with the NoP group.

In addressing the third objective, assessment of key ORT treatment outcomes was undertaken over the 5-year follow-up period. Overall, the findings indicate that the CP group was almost consistently associated with poorer ORT treatment outcomes compared with the NoP group. A significantly higher proportion of the CP group was deceased at 5-year follow-up. Whilst intentional self-harm (i.e. suicide) was a prominent cause of death in the NoP group, medical morbidity was a prominent cause of death in the CP group. Whilst biochemical drug screen

results indicated no group differences concerning illicit opioid use at study inception or at follow-up, a significantly higher proportion of the CP group was engaged in illicit cannabinoid use and non-medical benzodiazepine use at both study inception and follow-up. Increased therapeutic opioid dose was not associated with initiation of any illicit substance use but was significantly associated with continuation of opioid, benzodiazepine and cannabinoid misuse during the follow-up period, solely in the CP group. Increased dose was shown to be significantly protective of continuation of opioid misuse and predictive of continuation of benzodiazepine and cannabinoid misuse. Examination was undertaken of a variety of prescription items, issued at any point during the 5-year follow-up period, which would be considered to be indicative of severe and/or chronic morbidity. Concerning medical morbidity, aside from analgesics, there were no group differences at follow-up and no effects of time. Concerning psychiatric morbidity, a significantly higher proportion of the CP group was in receipt of anxiolytic medication, and a higher mean diazepam-equivalent dose, during the observation period compared with the NoP group. A significantly higher proportion of the CP group was admitted to psychiatric hospitals. A significantly smaller proportion of the CP group was admitted for the treatment of psychoactive substance use whilst a significantly higher proportion was admitted for the treatment of neurotic, stress-related and somatoform disorders and for mood disorders.

Chapter 4

Clinical profile, and univariate clinical predictors of long-term illicit substance use, in treatment-seeking, opioid-dependent patients with chronic pain: Comparison of groups based on patient-attributed direction of the causal relationship between opioid dependence and chronic pain

4.1 Introduction

The findings of the previous chapter suggest that treatment-seeking, opioid-dependent patients with comorbid chronic pain are associated with greater health burdens and poorer treatment outcomes than opioid-dependent patients with no pain. This comorbid group is generally considered to be an homogenous clinical population that receives standardised care within ORT programmes. This standardised approach may, however, prevent effective management of these conditions, since this comorbid group may be comprised of distinct clinical subgroups that have differing treatment requirements. For example, different disease trajectories leading to this comorbid presentation may be associated with differing ORT and analgesic requirements, and with distinct profiles of medical and psychiatric morbidities that may impact on the effectiveness of standardised treatment strategies. Chronic pain and opioid dependence are commonly-occurring comorbidities for a number of reasons. First, opioid dependence can develop as a consequence of chronic pain via the mechanisms of iatrogenic addiction to opioids or pseudoaddiction. Secondly, opioid-dependent patients are shown to be associated with a high risk of developing painful conditions through increased exposure to situations that result in physical trauma, violence and injury (NIDA, 2017) and, furthermore, pain may be more likely to develop in patients treated with long-term, high-dose opioids, of the magnitude prescribed in ORT programmes, in consequence of opioid-induced hyperalgesia.

It is possible that a proportion of patients in ORT programmes may have reached these clinical settings as a result of treatment or undertreatment for chronic pain and, furthermore, that patients entering ORT treatment facilities may have subsequently developed chronic pain problems as a function of ORT treatment. Opioid dependence is a chronic, relapsing condition and ORT programmes are associated with relatively poor recovery rates with small numbers

achieving long-term abstinence (Hser *et al.*, 2015). The delivery of effective treatment is dependent upon accurately profiling and responding to the clinical challenges associated with patients in ORT programmes and, as such, there is a need to establish whether patients whose opioid dependence resulted from chronic pain present with different clinical profiles and treatment requirements from patients whose chronic pain resulted from opioid dependence. Examining the temporal relationship between entries to treatment for these conditions is likely to be biased, since patients may be more likely to seek treatment for pain at an earlier stage of disease development than for opioid dependence. Furthermore, the temporal relationship between the onset of these conditions would not necessarily permit conclusions concerning the causal impact of one upon the other. Although associated with its own limitations, the patient-attributed direction of the causal relationship between chronic pain and opioid dependence may provide a more reliable indication of potential clinical subgroups within this comorbid population.

4.1.1 Objectives

The overarching aim of the research presented in this chapter was to establish whether patients whose attribution for the aetiology of their opioid use disorder resulted from chronic pain presented with different clinical profiles and treatment requirements from patients who attributed the development of chronic pain as a consequence of substance misuse. The author is not aware of this work having yet been addressed in the literature. The first objective was to establish groups based on the patient-attributed direction of the causal relationship between chronic pain and opioid dependence. The second objective was to evaluate whether these two groups were similar, or were distinct clinical populations. This was achieved by examining group differences in sociodemographic characteristics, substance use treatment outcomes, pain and dependence characteristics and presence of additional morbidities. The third objective was to examine whether these two groups were in receipt of similar treatment for opioid dependence and chronic pain or if treatment differed between groups at both study inception and during the follow-up period. The fourth objective was to evaluate the predictive capacity of clinical and treatment characteristics on long-term illicit or nonmedical substance use.

4.2 Group identification

The first objective was to establish groups based on the patient-attributed causal relationship between chronic pain (CP) and opioid use disorder (OUD). [Either the term, 'opioid dependence' or 'opioid dependence disorder' would have been preferred, in the interests of accuracy; however, since 'OD' and 'ODD' are established abbreviations, used to indicate overdose and

oppositional defiant disorder, respectively, the term 'opioid use disorder' (and the abbreviation, 'OUD') was used in the present chapter.] Just over two thirds of the cohort (69%, n=174) reported that they considered that CP had caused OUD (the ***CP→OUD group***) whilst the remainder (31%, n=78) reported that they considered that OUD had caused CP (the ***OUD→CP group***).

4.3 Comparison of the clinical presentation of both groups at study inception

The second objective was to evaluate whether these two groups presented as similar or distinct clinical populations. In an effort to address this second objective, group comparisons were undertaken for sociodemographic characteristics (4.3.1); patient-reported illicit substance use (4.3.2); pain and dependence characteristics (4.3.3); medical comorbidity (4.3.4); and psychiatric comorbidity (4.3.5).

4.3.1 Sociodemographic profile of each group at study inception

This section examines group differences at study inception (undertaken in 2005): demographic characteristics; educational attainment; employment status; residential stability; and family characteristics. Demographic characteristics are shown in ***Figure 4.1***. Deprivation status was calculated using the Scottish Index of Multiple Deprivation (SIMD). Quintiles 1-2 represented 'deprivation' and quintiles 3-5 represented 'affluence'.

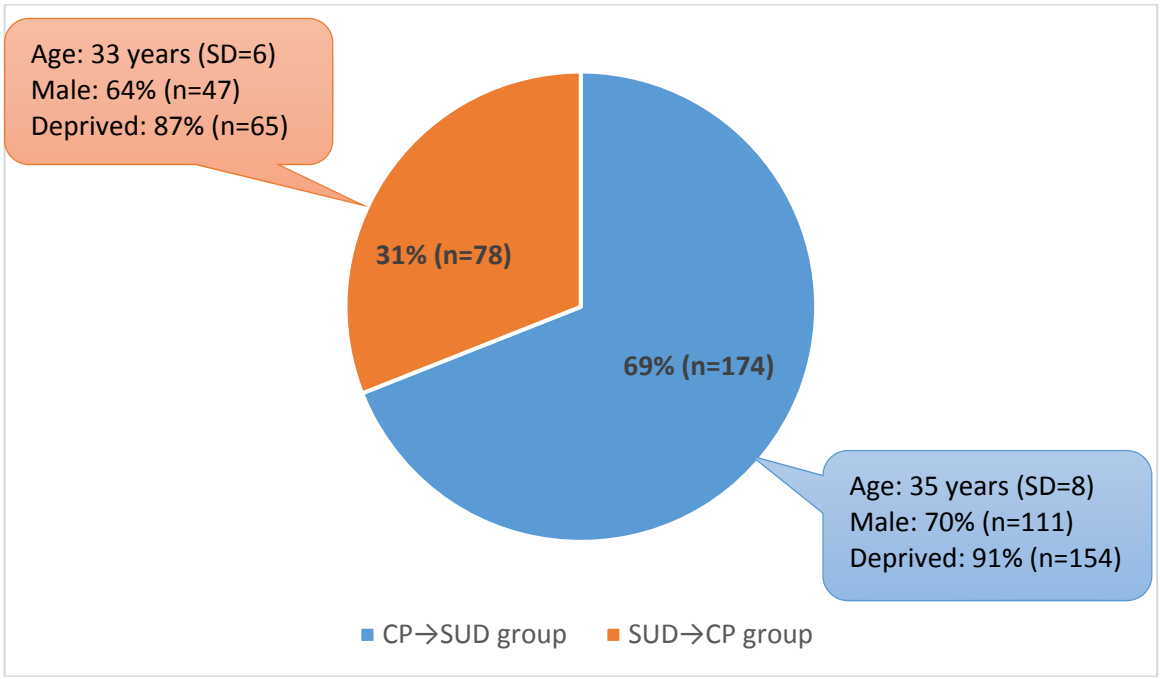


Figure 4.1: *Mean age, gender and socioeconomic distribution in each group.*

There were no significant group differences concerning gender or deprivation status but the CP→OUD group was statistically significantly older than the OUD→CP group (F(1,232)=5.676; p=0.018; η_p^2=0.024). Whilst statistically significant, in real terms this equates to a mean age difference of only 2 years.

Educational attainment and employment status are shown in ***Table 4.1a*** (categorical dependent variables) and ***Table 4.11b*** (continuous dependent variables).

Table 4.1a: *Group differences in educational attainment and employment status at study inception (categorical variables).*

Categorical variables	**CP→OUD**		**OUD→CP**	
	n	**%**	**n**	**%**
Educational attainment (n=222, 88%)	***χ^2(4)=3.301; p=0.509 (w=0.122)***			
None	86	57	44	61
O' Grades	39	26	15	21
Apprentice/SVQ/City & Guilds	4	3	1	1
Highers	7	5	7	10
College/University	14	9	5	7
Literacy/numeracy skills (n=225, 89%)	***χ^2(2)=0.531; p=0.767 (w=0.049)***			
Not good	19	13	7	10
OK	55	36	29	40
Good	78	51	37	50
Any paid work in past 30 days (n=217, 86%)	***χ^2(1)=1.883; p=0.140 (w=0.093)***			
Yes	8	5	7	10
No	142	95	60	90
Any work absence due to illness (n=15, 100%)	***χ^2(1)=1.759; p=0.231 (w=0.342)***			
Yes	1	12	3	43
No	7	88	4	57
Unemployed in past 30 days (n=213, 85%)	***χ^2(1)=1.142; p=0.188 (w=0.073)***			
Yes	113	77	55	83
No	34	23	11	17

Table 4.1b: *Group differences in employment characteristics at study inception (continuous variables).*

Continuous variables (Number of days in past 30 days)	**CP→OUD**		**OUD→CP**	
	$\bar{x}$	σ	$\bar{x}$	σ
Paid work (n=15, 100%)	***F(1,14)=0.000; p=0.990 (η_p^2=0.000)***			
	17.63	13.67	17.71	12.45
Absence due to sickness (n=15, 100%)	***F(1,14)=1.396; p=0.259 (η_p^2=0.097)***			
	0.13	0.35	2.29	5.19
Unemployed (n=168, 100%)	***F(1,167)=2.068; p=0.152 (η_p^2=0.012)***			
	30.00	0.00	29.69	2.29

There were no significant group differences in educational attainment or employment status. Both groups were characterised by poor educational attainment with more than half of each group having attained no formal qualifications and less than 20% of each group having attained qualifications beyond O'grades or equivalent. A very small proportion of each group had been in employment in the 30 days preceding assessment for a mean of 18 days in each group.

Residential stability and family characteristics are shown in ***Table 4.2***. There is a degree of missing data; however, data are assumed to be missing at random.

Table 4.2: *Group differences in home and family characteristics at study inception (categorical variables).*

Categorical variables	CP→OUD		OUD→CP	
	n	%	n	%
Frequency of changing address (n=187, 74%)	***$\chi^2(3)=4.112$; p=0.250 (w=0.148)***			
Never	35	28	12	20
Sometimes	68	54	31	51
Frequently	17	13	15	24
Very frequently	6	5	3	5
Time at current address (n=229, 91%)	***$\chi^2(5)=8.512$; p=0.130 (w=0.193)***			
< 1 month	10	6	6	8
1-6 months	17	11	7	10
6-12 months	20	13	17	24
1-3 years	44	28	13	18
3-5 years	22	14	14	20
5+ years	45	28	14	20
Lives alone or with others (n=230, 91%)	***$\chi^2(4)=4.399$; p=0.355 (w=0.138)***			
Alone	67	43	28	39
With partner	32	20	19	26
With family	47	30	25	34
With friends	8	5	1	1
Hostel	3	2	0	0
Has children (n=222, 88%)	***$\chi^2(1)=0.069$; p=0.793 (w=0.018)***			
Yes	125	83	61	85
No	25	17	11	15
Children live at home (n=183; 98%)	***$\chi^2(1)=5.070$; p=0.024 (w=0.166)***			
Yes	50	41	35	58
No	73	59	25	42

There were no significant group differences concerning residential stability or time at current address. More than half of each group lived either alone or with a partner; however, more than a third of each group lived with family, friends or in a hostel. More than 80% of each group had children but a high proportion of both groups reported that their children did not reside in the family home. Significantly more participants from the CP→OUD group reported that their children lived elsewhere.

4.3.2 Group differences in patient-reported illicit substance use at study inception

Group differences in patient-reported illicit substance use are shown in ***Table 4.3a*** (categorical dependent variables) and ***Table 4.3b*** (continuous dependent variables). Missing data are assumed to be missing at random.

Table 4.3a: *Group differences in patient-reported substance use at study inception (categorical variables).*

Categorical variables	**CP→OUD**		**OUD→CP**	
Patient-reported illicit use of:	**n**	**%**	**n**	**%**
Any substance (n=217, 86%)	***$\chi^2(1)=8.239$; p=0.001 (w=0.195)***			
Yes	133	89	67	100
No	17	11	0	0
Heroin (n=216, 86%)	***$\chi^2(1)=0.682$; p=0.249 (w=0.056)***			
Yes	60	40	31	46
No	89	60	36	54
Methadone (n=217, 86%)	***$\chi^2(1)=3.637$; p=0.041 (w=0.129)***			
Yes	45	30	29	43
No	105	70	38	57
Opioid analgesics (n=215, 85%)	***$\chi^2(1)=5.082$; p=0.022 (w=0.154)***			
Yes	18	12	16	24
No	131	88	50	76
Benzodiazepines (n=217, 86%)	***$\chi^2(1)=0.206$; p=0.380 (w=0.031)***			
Yes	49	33	24	36
No	101	67	43	64
Cannabinoids (n=215, 85%)	***$\chi^2(1)=4.047$; p=0.031 (w=0.137)***			
Yes	110	74	58	87
No	38	26	9	13

Table 4.3b *details group differences in patient-reported substance use characteristics at study inception (continuous variables).*

Continuous variables (Days use in past 30 days)	**CP→OUD**		**OUD→CP**	
	$\bar{x}$	σ	$\bar{x}$	σ
Heroin (n=91, 100%)	***F(1,90)=4.696; p=0.033 (η_p^2=0.050)***			
	6.63	8.76	11.06	10.13
Methadone (n=74, 100%)	***F(1,73)=4.404; p=0.039 (η_p^2=0.058)***			
	7.96	10.10	12.97	9.92
Opioid analgesics (n=34, 100%)	***F(1,33)=5.493; p=0.025 (η_p^2=0.147)***			
	8.56	11.11	1.94	2.05
Benzodiazepines (n=73, 100%)	***F(1,72)=0.052; p=0.820 (η_p^2=0.001)***			
	9.41	11.18	8.79	10.06
Cannabinoids (n=168, 100%)	***F(1,167)=0.101; p=0.751 (η_p^2=0.001)***			
	22.05	11.10	22.62	11.27

A significantly higher proportion of the OUD→CP group reported any illicit or nonmedical substance use in the 30 days prior to study inception. This was characterised by significantly higher proportions engaging in illicit use of methadone, opioid analgesics and cannabinoids. Furthermore, the OUD→CP group also reported using methadone on significantly more days than the CP→OUD group. Conversely, however, of those that reported misusing opioid analgesics, the CP→OUD group reported using them on significantly more days than the OUD→CP group. Whilst there was no significant difference concerning the proportion of each group engaging in illicit heroin use, the OUD→CP group reported using heroin on significantly more days than the CP→OUD group.

4.3.3 Group differences in pain and dependence characteristics

Group differences in pain and dependence characteristics at study inception are shown in ***Table 4.4*** (categorical variables) and ***Table 4.5*** (continuous variables).

Table 4.4: Pain and dependence characteristics at study inception (categorical variables)

Categorical variables In receipt of prescribed analgesic treatment	**CP→OUD** **n**	**%**	**OUD→CP** **n**	**%**
Pain at multiple sites (n=252, 100%)	***$\chi^2(1)=0.048$; p=0.827 (w=0.014)***			
Yes	38	22	18	23
No	136	78	60	77
Pain interference: daily activities (n=240, 95%)	***$\chi^2(1)=0.071$; p=0.790 (w=0.017)***			
Yes	125	76	58	77
No	40	24	17	23
Pain interference: sleep (n=251, 100%)	***$\chi^2(1)=0.810$; p=0.368 (w=0.057)***			
Yes	136	78	64	83
No	38	22	13	17
Stabilised in ORT treatment (n=243, 96%)	***$\chi^2(1)=9.103$; p=0.003 (w=0.194)***			
Yes	42	25	6	8
No	127	75	68	92
Excessive hyperhidrosis (n=252, 100%)	***$\chi^2(1)=0.147$; p=0.702 (w=0.025)***			
Yes	129	77	57	75
No	38	23	19	25
IV drug use in preceding 4 weeks (n=251, 100%)	***$\chi^2(1)=4.691$; p=0.030 (w=0.137)***			
Yes	18	10	16	21
No	155	90	62	79

Table 4.5: Pain and dependence characteristics at study inception (continuous variables)

Continuous variables (Days use in past 30 days)	**CP→OUD** $\bar{x}$	σ	**OUD→CP** $\bar{x}$	σ
Mean pain duration (months) (n=250, 99%)	***F(1,250)=12.543; p<0.001 (η_p^2=0.048)***			
	97.38	93.14	56.68	57.78
Mean pain intensity (n=251, 100%)	***F(1,250)=4.255; p=0.040 (η_p^2=0.017)***			
	64.42	20.99	58.47	21.29
Mean score for injecting risk (n=31, 12%)	***F(1,30)=4.542; p=0.042 (η_p^2=0.135)***			
	1.73	4.01	8.75	12.14

There were no group differences concerning pain at multiple sites or pain interference on daily activities or sleep quality. The CP→OUD group was, however, associated with a significantly higher duration of pain at study inception and a higher mean pain intensity (recorded on a 0-

100 numerical rating scale). There was no indication of group differences concerning physiological dependence severity as assessed by hyperhidrosis; however, a significantly higher proportion of the OUD→CP group had failed to stabilise in ORT treatment and were using drugs intravenously. Furthermore, the OUD→CP group was associated with a significantly higher health risk as a consequence of IV drug use.

4.3.4 Group differences in medical comorbidity at study inception and treatment characteristics during 5-year follow-up

Group difference in the physical health subscale score of the Maudsley Addiction Profile (MAP) is shown in ***Table 4.6a***.

Table 4.6a: *Group difference in the physical health subscale score of the Maudsley Addiction Profile at study inception.*

Continuous variables	**CP→OUD**		**OUD→CP**	
	$\bar{x}$	σ	$\bar{x}$	σ
MAP Physical Health score (n=248, 98%)	***F(1,247)=10.034; p=0.002 (η_p^2=0.039)***			
	16.08	7.49	19.39	7.88

Total scores on the MAP physical health subscale range from 0 to 40. The subscale is problem-scored; therefore, the OUD→CP group was associated with significantly poorer physical health than the CP→OUD group.

The individual items that were summed in the calculation of the physical health subscale score are shown in ***Table 4.6b***. The ten individual items comprising the physical health subscale were considered to be a family of tests and, therefore, the alpha was adjusted accordingly. Statistical significance was indicated by a p-value of 0.005 or less.

Table 4.6b: *Group differences on the individual items comprising the MAP physical health subscale at study inception.*

Categorical variables	**CP→OUD**		**OUD→CP**	
Patient-reported physical health problems:	**n**	**%**	**n**	**%**
Poor appetite (n=251, 100%)	***$\chi^2(2)=2.350$; p=0.309 (w=0.097)***			
Never	27	16	8	10
Rarely/sometimes	58	33	22	29
Often/always	89	51	47	61
Tiredness or fatigue (n=251, 100%)	***$\chi^2(2)=1.076$; p=0.584 (w=0.065)***			
Never	21	12	12	16
Rarely/sometimes	62	36	23	30
Often/always	91	52	42	54
Stomach pains (n=251, 100%)	***$\chi^2(2)=5.834$; p=0.054 (w=0.152)***			
Never	42	24	30	38
Rarely/sometimes	74	43	24	31
Often/always	57	33	24	31
Nausea (n=250, 99%)	***$\chi^2(2)=1.989$; p=0.370 (w=0.089)***			
Never	74	43	27	35
Rarely/sometimes	66	38	30	39
Often/always	33	19	20	26
Breathing difficulties (n=250, 99%)	***$\chi^2(2)=4.582$; p=0.101 (w=0.135)***			
Never	69	40	26	34
Rarely/sometimes	75	43	29	38
Often/always	29	17	22	28
Chest pain (n=250, 99%)	***$\chi^2(2)=0.177$; p=0.915 (w=0.027)***			
Never	79	46	38	49
Rarely/sometimes	69	40	30	38
Often/always	24	14	10	13
Joint or bone pain (n=249, 99%)	***$\chi^2(2)=1.748$; p=0.417 (w=0.084)***			
Never	28	16	18	23
Rarely/sometimes	53	31	24	31
Often/always	90	53	36	46
Muscle pain (n=251, 100%)	***$\chi^2(2)=4.619$; p=0.099 (w=0.136)***			
Never	47	27	31	40
Rarely/sometimes	58	34	25	32
Often/always	68	39	22	28
Numbness or tingling (n=251, 100%)	***$\chi^2(2)=1.218$; p=0.544 (w=0.070)***			
Never	63	36	23	30
Rarely/sometimes	57	33	30	39
Often/always	54	31	24	31
Tremors or shakes (n=251, 100%)	***$\chi^2(2)=2.655$; p=0.265 (w=0.103)***			
Never	78	45	28	36
Rarely/sometimes	65	37	29	38
Often/always	31	18	20	26

Table 4.6b shows that the significantly higher MAP physical health subscale score in the OUD→CP group was not mediated by any specific health condition(s) but, rather, was indicative of poorer overall health in this group.

Table 4.7a shows the proportion of each group in receipt of prescribed medication indicative of severe and/or chronic medical morbidity and the proportion of each group admitted to general hospitals for the treatment of medical morbidity during the 5-year follow-up period. ***Table 4.7b*** shows the number of admissions and the total number of nights spent in general hospitals for each group during the follow-up period.

Table 4.7a: *Group differences in prescription medication indicative of severe and/or chronic medical morbidity and general hospital admissions for the treatment of medical morbidity during the follow-up period.*

	CP→OUD		OUD→CP	
	n	**%**	**n**	**%**
Rx for medical morbidity (n=252, 100%)	***$\chi^2(1)=0.283$; p=0.595 (w=0.034)***			
Yes	162	93	74	95
No	12	7	4	5
Rx excluding analgesia (n=252, 100%)	***$\chi^2(1)=0.628$; p=0.428 (w=0.050)***			
Yes	155	89	72	92
No	19	11	6	8
Admission to general hospitals (n=252, 100%)	***$\chi^2(1)=1.011$; p=0.315 (w=0.063)***			
Yes	81	47	31	40
No	93	53	47	60

Table 4.7b: *Group differences in the number of admissions and total number of nights spent in general hospitals during the follow-up period.*

	CP→OUD		OUD→CP	
	$\bar{x}$	σ	$\bar{x}$	σ
Mean number of admissions (n=108, 96%)	***F(1,107)=8.955; p=0.003 (η_p^2=0.078)***			
	2.63	2.28	4.63	4.66
Mean number of nights *(n=108, 96%)*	***F(1,107)=9.617; p=0.002 (η_p^2=0.083)***			
	15.03	21.44	45.27	79.44

There were no group differences concerning receipt of prescribed medication for the treatment of medical morbidities with most participants in each group having been in receipt of prescriptions at some point during the follow-up period, even on exclusion of analgesic medication. Whilst there were no group differences in the proportion of participants admitted to general hospitals, of those that were admitted, the OUD→CP group was associated with significantly more admissions and more nights spent in hospital.

4.3.5 Group differences in psychiatric comorbidity at study inception and treatment characteristics during 5-year follow-up

Group differences in psychiatric 'caseness' at study inception are shown in ***Table 4.8a*** and the corresponding subscale scores are shown in ***Table 4.8b***. psychiatric 'caseness', assessed by the GHQ-28 and the CORE, were considered to be a family of tests and, therefore, the alpha was adjusted accordingly. Statistical significance was indicated by a p-value of 0.025 or less.

Table 4.8a: *Group differences in psychiatric 'caseness' at study inception using standardised assessment instruments.*

Standardised assessment instruments	**CP→OUD**		**OUD→CP**	
	n	**%**	**n**	**%**
Psychiatric caseness [GHQ] (n=207, 82%)	***$\chi^2(1)=4.935$; p=0.018 (w=0.154)***			
Clinical	80	57	49	73
Non-clinical	60	43	18	27
Psychiatric caseness [CORE] (242, 96%)	***$\chi^2(1)=4.970$; p=0.017 (w=0.143)***			
Clinical (10-40)	115	69	63	83
Non-clinical (0-9)	51	31	13	17
Social phobia caseness [SPDQ] (n=215, 85%)	***$\chi^2(1)=11.481$; p=0.001 (w=0.231)***			
Yes	56	38	42	63
No	92	62	25	37
PTSD caseness [IES] (n=215, 85%)	***$\chi^2(1)=1.537$; p=0.215 (w=0.079)***			
Yes	67	39	36	47
No	105	61	40	53

Table 4.8a shows significantly higher prevalence of psychiatric 'caseness' in the OUD→CP group compared with the CP→OUD group. Slightly higher proportions were identified on using the CORE compared with the GHQ-28. Prevalence of social phobia was also significantly higher in the OUD→CP group compared with the CP→OUD group. There was no difference between groups concerning the prevalence of PTSD.

Table 4.8b: *Group differences in scores on psychiatric subscales at study inception.*

Continuous variables	**CP→OUD**		**OUD→CP**	
	$\bar{x}$	σ	$\bar{x}$	σ
Baseline GHQ-28 subscale				
Social Dysfunction (n=239, 95%)	*F(1,238)=6.474; p=0.012 (η_p^2=0.027)*			
	7.99	3.12	9.09	3.13
Severe Depression (n=239, 95%)	*F(1,442)=1.086; p=0.298 (η_p^2=0.005)*			
	4.73	4.70	5.42	4.93
Somatic Symptoms (n=239, 95%)	*F(1,238)=34.133; p=0.043 (η_p^2=0.017)*			
	7.77	3.83	8.86	3.91
Anxiety/Insomnia (n=239, 95%)	*F(1,238)=4.180; p=0.042 (η_p^2=0.017)*			
	8.45	4.99	9.84	4.73
CORE subscales				
Subjective Wellbeing (n=242, 96%)	*F(1,241)=1.570; p=0.211 (η_p^2=0.006)*			
	7.27	4.41	8.04	5.59
Problems/Symptoms (n=242, 96%)	*F(1,241)=26.491; p=0.011 (η_p^2=0.026)*			
	24.00	11.43	29.99	25.18
Life Functioning (n=242, 96%)	*F(1,241)=5.073; p=0.025 (η_p^2=0.021)*			
	17.89	10.82	21.50	13.06
Risk/Harm (n=242, 96%)	*F(1,241)=4.495; p=0.035 (η_p^2=0.018)*			
	2.14	3.15	3.09	3.40
IES subscales (PTSD)				
Intrusion (n=248, 98%)	*F(1,247)=1.893; p=0.170 (η_p^2=0.008)*			
	12.11	12.93	14.55	12.78
Avoidance (n=248, 98%)	*F(1,247)=4.109; p=0.044 (η_p^2=0.016)*			
	12.12	13.21	15.96	14.91

Table 4.8b shows that OUD→CP group was associated with significantly higher subscale scores on three of the four GHQ-28 subscales (social dysfunction, somatic symptoms and anxiety/insomnia). There was no group difference on the severe depression subscale. Similarly, the OUD→CP group was associated with significantly higher subscale scores on three of the four CORE subscales (problems/symptoms, life functioning and risk/harm). The life functioning subscale is problem-scored; therefore, higher scores are associated with poorer life functioning. There was no group difference on the subjective wellbeing subscale.

Table 4.9a shows the proportion of each group in receipt of prescribed medication indicative of severe and/or chronic psychiatric morbidity and the proportion of each group admitted to

psychiatric hospitals for the treatment of psychiatric morbidity during the 5-year follow-up period. ***Table 4.9b*** shows the number of admissions and the total number of nights spent in psychiatric hospitals for each group during the follow-up period.

Table 4.9a: *Group differences in prescription medication indicative of severe and/or chronic psychiatric morbidity and psychiatric hospital admissions for the treatment of psychiatric morbidity during the follow-up period.*

	CP→OUD		OUD→CP	
	n	**%**	**n**	**%**
Rx for psychiatric morbidity (n=252, 100%)	***$\chi^2(1)=0.021$; p=0.885 (w=0.009)***			
Yes	155	89	69	89
No	19	11	9	11
Rx for anxiety disorders (n=252, 100%)	***$\chi^2(1)=0.480$; p=0.489 (w=0.044)***			
Yes	115	66	55	71
No	59	34	23	29
Rx for depressive disorders (n=252, 100%)	***$\chi^2(1)=0.085$; p=0.770 (w=0.018)***			
Yes	128	74	56	72
No	46	26	22	28
Rx for psychotic disorders (n=252, 100%)	***$\chi^2(1)=0.021$; p=0.885 (w=0.009)***			
Yes	32	18	9	12
No	142	82	69	88
Admission to psychiatric hospitals (n=252, 100%)	***$\chi^2(1)=4.414$; p=0.036 (w=0.132)***			
Yes	34	20	7	9
No	140	80	71	91

Table 4.9b: *Group differences in the number of admissions and total number of nights spent in psychiatric hospitals during the follow-up period.*

	CP→OUD		OUD→CP	
	$\bar{x}$	σ	$\bar{x}$	σ
Mean number of admissions (n=41, 100%)	***F(1,40)=0.240; p=0.627 (η_p^2=0.006)***			
	2.12	1.49	2.43	1.72
Mean number of nights ***(n=108, 96%)***	***F(1,107)=9.617; p=0.002 (η_p^2=0.083)***			
	23.12	22.09	33.80	49.00

There were no group differences concerning receipt of prescribed medication for the treatment of psychiatric morbidities with most participants in each group having been in receipt of prescriptions at some point during the follow-up period. Similarly, there were no group differences concerning prescribing for specific conditions with the majority of both groups having been in receipt of medication for the treatment of anxiety and depressive disorders and a smaller proportion of each group having been in receipt of medication for the treatment of psychotic disorders. A significantly higher proportion of the CP→OUD group had been admitted to psychiatric hospitals during the follow-up period but there were no group differences concerning mean number of admissions during this period. Of those that were admitted, the OUD→CP group was associated with a significantly elevated mean number of nights' stay in hospital during this period.

4.3.6 Summary of section findings: Clinical distinctiveness of groups

These findings suggest that these two groups present as clinically distinct treatment populations. The CP→OUD group was characterised by elevated illicit cannabinoid use and more frequent nonmedical use of opioid analgesics, whilst the OUD→CP group was characterised by elevated overall drug misuse and, specifically, illicit use of opioids. Whilst the CP→OUD group was associated with poorer pain-related health, the OUD→CP group was associated with poorer overall physical health and more severe psychiatric symptoms, particularly general functioning and neurotic disorders.

4.4 Treatment characteristics of each group at study inception and during the follow-up period

The third objective was to examine whether these two groups were in receipt of similar treatment for opioid dependence and chronic pain or if treatment differed between groups at both study inception and during the follow-up period. Group differences in treatment characteristics were examined at study inception and during the observation period. Examination of prescribed medication focused on ORT treatment and analgesic treatment. Benzodiazepines were included in the evaluation of ORT treatment for two principal reasons: first, it is a common adjunct used in the treatment of opioid-dependent patients; secondly, since there were a number of group differences concerning neurotic disorders, examination of benzodiazepine treatment was considered to be of interest. Examination of analgesic prescribing focused solely on opioid analgesic treatment for a number of reasons. First, non-steroidal anti-inflammatory drugs (NSAIDs) are commonly purchased over-the-counter (OTC);

therefore, inclusion of NSAIDs could bias findings. Secondly, prescribed NSAIDs are unlikely to be used in the treatment of chronic pain due to severe gastric side effects and other risks, such as gastric haemorrhage and renal failure, associated with chronic exposure. Thirdly, it is not possible to compare different NSAIDs using equianalgesic calculations. Fourthly, whilst 18% (n=45) of the entire cohort was in receipt of gabapentin and/or amitriptyline, indicative of possible treatment for neuropathic pain, these medications may be used in the treatment of other conditions and, furthermore, they cannot be compared using equianalgesic calculations. Whilst it is true that some weak opioids can be purchased OTC and opioids can also be used for other indications (e.g. codeine for the treatment of diarrhoea or for cough), the combination of these issues provides a strong argument for solely examining opioid analgesics.

4.4.1 Group differences in treatment characteristics at study inception

Characteristics associated with prescribed ORT and analgesic medications and patient satisfaction with ORT and analgesic treatment are shown in ***Table 4.10a*** (categorical dependent variables) and ***Table 4.10b*** (continuous dependent variables).

Table 4.10a: *Receipt of prescribed analgesic opioid and benzodiazepine medication and patient-attributed physician attitude to pain problem at study inception*

	CP→OUD		OUD→CP	
	n	**%**	**n**	**%**
Opioid analgesics	***$\chi^2(1)=0.520$; p=0.471 (w=0.045)***			
Yes	19	11	11	14
No	155	89	67	86
Any benzodiazepine treatment	***$\chi^2(1)=0.735$; p=0.391 (w=0.054)***			
Yes	86	49	34	44
No	88	51	44	56
Patient-attributed physician attitude	***$\chi^2(1)=0.940$; p=0.332 (w=0.069)***			
Pain problem taken seriously	89	63	30	56
Pain problem not taken seriously	52	37	24	44

Table 4.10b: *Morphine-equivalent opioid doses, diazepam-equivalent benzodiazepine dose and patient satisfaction score relating to ORT treatment at study inception*

Continuous variables	**CP→OUD**		**OUD→CP**	
	$\bar{x}$	σ	$\bar{x}$	σ
Morphine-equivalent methadone dose	***F(1,248)=0.353; p=0.553 (η_p^2=0.001)***			
Mean dose	104	54	108	54
Morphine-equivalent opioid analgesic dose	***F(1,29)=4.250; p=0.049 (η_p^2=0.132)***			
Mean dose	64	61	25	15
Morphine-equivalent total opioid dose	***F(1,249)=0.164; p=0.686 (η_p^2=0.001)***			
Mean dose	109	57	112	54
Diazepam-equivalent benzodiazepine dose	***F(1,119)=0.348; p=0.556 (η_p^2=0.003)***			
Mean dose	34	28	31	26
ORT treatment satisfaction total score †	***F(1,87)=5.582; p=0.019 (η_p^2=0.023)***			
Mean dose	22.51	5.93	20.56	6.07

† Obtained using the standardised Treatment Perception Questionnaire (TPQ). Higher scores (on the 0-40 scale) indicate greater satisfaction with treatment received.

There were no significant group differences concerning the proportion in receipt of opioid analgesics; however, of those in receipt of prescribed opioid analgesics, the CP→OUD group was in receipt of a significantly higher morphine-equivalent daily dose than the OUD→CP group. Despite this finding, there was no significant group difference concerning satisfaction with treatment for pain problems. There were no significant group differences concerning methadone dose, receipt of benzodiazepines or diazepam-equivalent daily benzodiazepine dose. The OUD→CP group was, however, significantly less satisfied with ORT treatment. There was no significant group difference associated with total opioid dose (i.e. opioid analgesic dose plus ORT dose).

4.4.2 Group differences in opioid treatment during the follow-up period

The proportion of each group in receipt of increasing prescription opioid doses during the follow-up period is shown in ***Table 4.11***.

Table 4.11: *Proportion of each group whose opioid dose increased during the follow-up period*

Type of opioid prescription	**CP→OUD group**		**OUD→CP group**	
	n	**%**	**n**	**%**
Opioid analgesics	14	30	12	38
ORT medication	89	51	42	54
Total opioids (i.e. analgesics plus ORT drugs)	91	52	45	58

4.4.3 Summary of section findings: Treatment characteristics

Of those in receipt of prescribed opioid analgesics, the CP→OUD group was in receipt of a significantly higher morphine-equivalent daily dose than the OUD→CP group but there was no significant group difference concerning satisfaction with treatment for pain problems. There were no significant group differences concerning methadone dose, receipt of benzodiazepines or diazepam-equivalent daily benzodiazepine dose; however, the OUD→CP group was, significantly less satisfied with ORT treatment. There were no statistically significant differences concerning the proportion of each group that was in receipt of increasing doses of opioid medication during the follow-up period.

4.5 Univariate predictors of illicit and nonmedical substance use

The fourth objective was to evaluate the predictive capacity of clinical and treatment characteristics on long-term illicit or nonmedical substance use. Sociodemographic and clinical characteristics at study inception and changes in opioid treatment during the follow-up period were entered as univariate predictors of long-term illicit and nonmedical substance use. Two outcome variables were examined. First, prediction of inception of illicit substance use during the follow-up period was undertaken, compared with abstinence at both study inception and 5-year follow-up. Secondly, prediction of continued substance use was undertaken, compared with cessation of use during the follow-up period.

4.5.1 Sociodemographic characteristics

The sociodemographic characteristics examined in this section were selected based on indications of their relevance to ORT treatment outcomes, as discussed throughout the literature.

Table 4.12a: *Univariate predictors (sociodemographic characteristics) of initiation of illicit opioid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Male gender				
Overall	101	0.789	0.330-1.887	0.594
CP→OUD group	74	0.563	0.193-1.643	0.293
OUD→CP group	27	1.833	0.374-8.984	0.455
Each increasing year of age				
Overall	101	0.942	0.885-1.003	0.060
CP→OUD group	74	0.933	0.870-1.000	0.049
OUD→CP group	27	1.007	0.853-1.189	0.930
Socioeconomic deprivation †				
Overall	109	0.939	0.238-3.704	0.929
CP→OUD group	80	1.242	0.235-6.565	0.798
OUD→CP group	29	0.500	0.040-6.218	0.590
Lives alone				
Overall	100	0.782	0.349-1.753	0.550
CP→OUD group	73	0.709	0.277-1.819	0.475
OUD→CP group	27	1.050	0.214-5.158	0.952
Has children				
Overall	93	1.533	0.433-5.430	0.508
CP→OUD group	67	1.435	0.350-5.893	0.616
OUD→CP group	26	1.667	0.092-30.060	0.729
Children live without the family home				
Overall	80	0.817	0.338-1.974	0.653
CP→OUD group	56	0.724	0.248-2.111	0.554
OUD→CP group	24	1.750	0.261-11.737	0.564

† Calculated using the Scottish Index of Multiple Deprivation (SIMD), with quintiles 1-2 representing 'deprivation' and quintiles 3-5 representing 'affluence'.

Table 4.12b: *Univariate predictors (sociodemographic characteristics) of continued illicit opioid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Male gender				
Overall	95	0.631	0.243-1.641	0.345
CP→OUD group	62	0.583	0.187-1.822	0.353
OUD→CP group	33	0.694	0.115-4.203	0.694
Each increasing year of age				
Overall	96	0.988	0.940-1.038	0.633
CP→OUD group	63	0.973	0.921-1.028	0.334
OUD→CP group	33	1.123	0.966-1.305	0.130
Socioeconomic deprivation †				
Overall	99	1.627	0.310-8.533	0.565
CP→OUD group	65	1.652	0.218-12.545	0.627
OUD→CP group	34	Not computed – insufficient data		
Lives alone				
Overall	95	0.992	0.423-2.327	0.985
CP→OUD group	62	0.739	0.266-2.054	0.562
OUD→CP group	33	2.500	0.426-14.657	0.310
Has children				
Overall	93	0.729	0.209-2.537	0.619
CP→OUD group	60	0.960	0.207-4.462	0.958
OUD→CP group	33	0.475	0.048-4.740	0.526
Children live without the family home				
Overall	77	2.400	0.889-6.478	0.084
CP→OUD group	51	2.812	0.820-9.652	0.100
OUD→CP group	26	1.667	0.303-9.157	0.557

† Calculated using the Scottish Index of Multiple Deprivation (SIMD), with quintiles 1-2 representing 'deprivation' and quintiles 3-5 representing 'affluence'.

Table 4.13a: *Univariate predictors (sociodemographic characteristics) of initiation of nonmedical benzodiazepine use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Male gender				
Overall	80	1.152	0.428-3.105	0.779
CP→OUD group	61	1.867	0.578-6.025	0.296
OUD→CP group	19	0.286	0.039-2.114	0.220
Each increasing year of age				
Overall	80	1.023	0.961-1.088	0.477
CP→OUD group	61	1.016	0.949-1.087	0.647
OUD→CP group	19	1.047	0.894-1.226	0.568
Socioeconomic deprivation †				
Overall	86	0.770	0.140-4.236	0.764
CP→OUD group	65	0.421	0.046-3.859	0.444
OUD→CP group	21	Not computed – insufficient data		
Lives alone				
Overall	80	0.674	0.252-1.800	0.431
CP→OUD group	61	0.450	0.149-1.360	0.157
OUD→CP group	19	Not computed – insufficient data		
Has children				
Overall	76	0.584	0.112-3.049	0.524
CP→OUD group	58	1.542	0.235-10.132	0.652
OUD→CP group	18	Not computed – insufficient data		
Children live without the family home				
Overall	65	0.806	0.294-2.212	0.675
CP→OUD group	51	0.702	0.218-2.258	0.552
OUD→CP group	14	1.875	0.204-17.269	0.579

† Calculated using the Scottish Index of Multiple Deprivation (SIMD), with quintiles 1-2 representing 'deprivation' and quintiles 3-5 representing 'affluence'.

Table 4.13b: *Univariate predictors (sociodemographic characteristics) of continued nonmedical benzodiazepine use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Male gender				
Overall	115	0.665	0.272-1.622	0.370
CP→OUD group	75	1.134	0.400-3.216	0.814
OUD→CP group	40	0.145	0.016-1.296	0.084
Each increasing year of age				
Overall	116	0.947	0.897-0.999	0.046
CP→OUD group	76	0.939	0.883-0.998	0.043
OUD→CP group	40	0.980	0.861-1.116	0.765
Socioeconomic deprivation †				
Overall	121	2.882	0.766-10.836	0.117
CP→OUD group	80	5.444	0.540-54.927	0.151
OUD→CP group	41	2.182	0.378-12.583	0.383
Lives alone				
Overall	114	0.354	0.161-0.780	0.010
CP→OUD group	74	0.453	0.173-1.189	0.108
OUD→CP group	40	0.212	0.052-0.870	0.031
Has children				
Overall	109	1.633	0.555-4.806	0.373
CP→OUD group	69	1.000	0.267-3.745	>0.999
OUD→CP group	40	6.818	0.636-73.059	0.113
Children live without the family home				
Overall	91	1.093	0.447-2.670	0.846
CP→OUD group	56	0.725	0.225-2.334	0.590
OUD→CP group	35	2.000	0.471-8.494	0.348

† Calculated using the Scottish Index of Multiple Deprivation (SIMD), with quintiles 1-2 representing 'deprivation' and quintiles 3-5 representing 'affluence'.

Table 4.14a: *Univariate predictors (sociodemographic characteristics) of initiation of illicit cannabinoid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Male gender				
Overall	101	0.468	0.193-1.133	0.092
CP→OUD group	65	0.816	0.246-2.707	0.740
OUD→CP group	36	0.094	0.018-0.488	0.005
Each increasing year of age				
Overall	101	0.968	0.919-1.020	0.224
CP→OUD group	65	0.943	0.884-1.007	0.080
OUD→CP group	36	0.962	0.850-1.088	0.537
Socioeconomic deprivation †				
Overall	103	0.294	0.032-2.730	0.282
CP→OUD group	65	Not computed – insufficient data		
OUD→CP group	37	0.154	0.012-1.927	0.147
Lives alone				
Overall	100	0.723	0.324-1.612	0.428
CP→OUD group	64	1.050	0.351-3.141	0.930
OUD→CP group	36	0.108	0.012-0.978	0.048
Has children				
Overall	95	2.581	0.852-7.817	0.094
CP→OUD group	60	4.062	0.938-17.587	0.061
OUD→CP group	35	1.184	0.192-7.320	0.856
Children live without the family home				
Overall	80	1.000	0.409-2.446	>0.999
CP→OUD group	52	0.667	0.182-2.437	0.540
OUD→CP group	28	Not computed – insufficient data		

† Calculated using the Scottish Index of Multiple Deprivation (SIMD), with quintiles 1-2 representing 'deprivation' and quintiles 3-5 representing 'affluence'.

Table 4.14b: *Univariate predictors (sociodemographic characteristics) of continued illicit cannabinoid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Male gender				
Overall	87	0.963	0.342-2.706	0.942
CP→OUD group	64	1.591	0.1483-5.237	0.445
OUD→CP group	23	0.225	0.021-2.356	0.213
Each increasing year of age				
Overall	88	0.992	0.932-1.057	0.811
CP→OUD group	65	0.975	0.909-1.045	0.474
OUD→CP group	23	1.064	0.885-1.280	0.507
Socioeconomic deprivation †				
Overall	92	3.026	0.840-10.898	0.090
CP→OUD group	67	2.250	0.451-11.222	0.323
OUD→CP group	25	4.875	0.430-55.292	0.201
Lives alone				
Overall				
CP→OUD group	87	0.538	0.213-1.360	0.190
OUD→CP group	64	0.387	0.127-1.181	0.095
	23	1.111	0.190-6.492	0.907
Has children				
Overall	83	0.470	0.052-4.245	0.501
CP→OUD group	60	Not computed – insufficient data		
OUD→CP group	23	Not computed – insufficient data		
Children live without the family home				
Overall	72	1.615	0.576-4.528	0.362
CP→OUD group	51	1.371	0.384-4.894	0.626
OUD→CP group	21	2.667	0.434-16.390	0.290

† Calculated using the Scottish Index of Multiple Deprivation (SIMD), with quintiles 1-2 representing 'deprivation' and quintiles 3-5 representing 'affluence'.

4.5.2 Physical health and pain characteristics

The impact of physical health was examined using the MAP physical health subscale total score; in addition, several pain-related characteristics were obtained from the BPI-SF.

Table 4.15a: *Univariate predictors (physical health, pain characteristics and pain treatment perception) of initiation of illicit opioid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Each incremental increase on the MAP physical health subscale score				
Overall	108	1.032	0.982-1.084	0.213
CP→OUD group	80	1.077	1.011-1.148	0.021
OUD→CP group	28	0.928	0.837-1.029	0.157
Each increasing month of duration of pain				
Overall	108	0.998	0.994-1.003	0.485
CP→OUD group	79	0.997	0.992-1.002	0.242
OUD→CP group	29	1.004	0.994-1.015	0.432
Each incremental increase on the pain intensity rating scale				
Overall	107	1.023	1.003-1.043	0.022
CP→OUD group	77	1.026	1.001-1.052	0.040
OUD→CP group	30	1.018	0.985-1.051	0.291
Patient-reported pain interference on sleep				
Overall	109	0.933	0.338-2.580	0.894
CP→OUD group	80	1.276	0.402-4.049	0.679
OUD→CP group	29	0.308	0.028-3.376	0.335
Patient-reported pain interference on daily activities				
Overall	103	1.477	0.565-3.864	0.427
CP→OUD group	76	1.800	0.591-5.479	0.301
OUD→CP group	27	0.800	0.111-5.772	0.825
Patient perception that pain problem was taken seriously by treating physician				
Overall	89	0.016	0.137-0.817	0.016
CP→OUD group	66	0.291	0.103-0.825	0.020
OUD→CP group	23	0.500	0.088-2.841	0.434

Table 4.15b: *Univariate predictors (physical health, pain characteristics and pain treatment perception) of continued illicit opioid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Each incremental increase on the MAP physical health subscale score				
Overall	100	1.009	0.957-1.064	0.735
CP→OUD group	66	1.014	0.950-1.082	0.685
OUD→CP group	34	0.989	0.901-1.085	0.817
Each increasing month of duration of pain				
Overall	102	0.997	0.992-1.002	0.283
CP→OUD group	68	0.998	0.992-1.003	0.427
OUD→CP group	34	1.011	0.983-1.039	0.455
Each incremental increase on the pain intensity rating scale				
Overall	100	0.992	0.972-1.011	0.406
CP→OUD group	67	0.997	0.975-1.019	0.762
OUD→CP group	33	0.982	0.938-1.028	0.442
Patient-reported pain interference on sleep				
Overall	102	2.787	1.027-7.564	0.044
CP→OUD group	68	3.431	1.069-11.014	0.038
OUD→CP group	34	0.917	0.083-10.140	0.943
Patient-reported pain interference on daily activities				
Overall	98	0.560	0.198-1.584	0.274
CP→OUD group	64	0.509	0.141-1.844	0.304
OUD→CP group	34	0.735	0.122-4.434	0.737
Patient perception that pain problem was taken seriously by treating physician				
Overall	81	0.618	0.236-1.616	0.326
CP→OUD group	56	1.227	0.394-3.815	0.724
OUD→CP group	25	0.135	0.013-1.449	0.098

Table 4.16a: *Univariate predictors (physical health, pain characteristics and pain treatment perception) of initiation of nonmedical benzodiazepine use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Each incremental increase on the MAP physical health subscale score				
Overall	85	1.017	0.951-1.087	0.629
CP→OUD group	65	1.051	0.967-1.143	0.242
OUD→CP group	20	0.961	0.850-1.087	0.529
Each increasing month of duration of pain				
Overall	86	1.001	0.996-1.007	0.703
CP→OUD group	66	1.000	0.994-1.007	0.879
OUD→CP group	20	1.002	0.986-1.018	0.817
Each incremental increase on the pain intensity rating scale				
Overall	86	0.996	0.974-1.018	0.714
CP→OUD group	66	0.999	0.974-1.026	0.959
OUD→CP group	20	0.983	0.941-1.027	0.446
Patient-reported pain interference on sleep				
Overall	86	1.589	0.526-4.806	0.412
CP→OUD group	66	2.171	0.626-7.530	0.222
OUD→CP group	20	0.563	0.043-7.442	0.662
Patient-reported pain interference on daily activities				
Overall	83	1.077	0.374-3.101	0.891
CP→OUD group	63	1.247	0.384-4.043	0.713
OUD→CP group	20	0.714	0.054-9.497	0.799
Patient perception that pain problem was taken seriously by treating physician				
Overall	74	0.616	0.230-1.648	0.334
CP→OUD group	57	0.513	0.161-1.633	0.258
OUD→CP group	17	1.500	0.181-12.459	0.707

Table 4.16b: *Univariate predictors (physical health, pain characteristics and pain treatment perception) of continued nonmedical benzodiazepine use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Each incremental increase on the MAP physical health subscale score				
Overall	122	0.981	0.938-1.025	0.388
CP→OUD group	81	0.989	0.936-1.044	0.680
OUD→CP group	41	0.963	0.891-1.041	0.339
Each increasing month of duration of pain				
Overall	123	0.998	0.994-1.002	0.377
CP→OUD group	81	1.000	0.996-1.005	0.912
OUD→CP group	42	0.986	0.974-0.998	0.023
Each incremental increase on the pain intensity rating scale				
Overall	121	0.985	0.967-1.003	0.108
CP→OUD group	79	0.990	0.968-1.011	0.341
OUD→CP group	42	0.974	0.940-1.009	0.145
Patient-reported pain interference on sleep				
Overall	124	1.048	0.402-2.733	0.924
CP→OUD group	82	1.278	0.429-3.808	0.659
OUD→CP group	42	0.462	0.047-4.571	0.509
Patient-reported pain interference on daily activities				
Overall	117	0.409	0.140-1.197	0.103
CP→OUD group	77	0.438	0.110-1.749	0.243
OUD→CP group	40	0.375	0.068-2.080	0.262
Patient perception that pain problem was taken seriously by treating physician				
Overall	96	0.652	0.279-1.526	0.324
CP→OUD group	65	0.706	0.247-2.021	0.516
OUD→CP group	31	0.615	0.135-2.815	0.531

Table 4.17a: *Univariate predictors (physical health, pain characteristics and pain treatment perception) of initiation of illicit cannabinoid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Each incremental increase on the MAP physical health subscale score				
Overall	104	0.955	0.908-1.005	0.078
CP→OUD group	67	0.986	0.917-1.060	0.699
OUD→CP group	37	0.954	0.872-1.044	0.309
Each increasing month of duration of pain				
Overall	105	1.004	0.999-1.009	0.102
CP→OUD group	67	1.001	0.995-1.007	0.677
OUD→CP group	38	0.998	0.983-1.013	0.755
Each incremental increase on the pain intensity rating scale				
Overall	105	0.989	0.970-1.009	0.289
CP→OUD group	67	0.991	0.965-1.017	0.485
OUD→CP group	38	0.988	0.950-1.026	0.525
Patient-reported pain interference on sleep				
Overall	106	0.972	0.333-2.839	0.959
CP→OUD group	68	1.667	0.470-5.906	0.429
OUD→CP group	38	0.800	0.065-9.844	0.862
Patient-reported pain interference on daily activities				
Overall	98	0.524	0.181-1.517	0.234
CP→OUD group	63	0.907	0.245-3.357	0.883
OUD→CP group	35	0.242	0.034-1.727	0.157
Patient perception that pain problem was taken seriously by treating physician				
Overall	92	0.397	0.167-0.945	0.037
CP→OUD group	60	0.153	0.031-0.754	0.021
OUD→CP group	32	0.220	0.037-1.296	0.094

Table 4.17b: *Univariate predictors (physical health, pain characteristics and pain treatment perception) of continued illicit cannabinoid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Each incremental increase on the MAP physical health subscale score				
Overall	90	0.968	0.913-1.027	0.285
CP→OUD group	66	0.952	0.883-1.025	0.193
OUD→CP group	24	1.012	0.911-1.124	0.825
Each increasing month of duration of pain				
Overall	91	1.001	0.996-1.006	0.742
CP→OUD group	67	1.001	0.995-1.006	0.806
OUD→CP group	24	0.999	0.987-1.010	0.814
Each incremental increase on the pain intensity rating scale				
Overall	89	0.988	0.967-1.010	0.279
CP→OUD group	65	0.983	0.956-1.011	0.240
OUD→CP group	24	0.978	0.936-1.022	0.316
Patient-reported pain interference on sleep				
Overall	91	0.599	0.196=1.834	0.369
CP→OUD group	67	0.313	0.063-1.541	0.153
OUD→CP group	24	2.062	0.277-15.357	0.480
Patient-reported pain interference on daily activities				
Overall	90	3.365	1.218-9.298	0.019
CP→OUD group	65	2.083	0.573-7.570	0.265
OUD→CP group	25	7.200	1.066-48.639	0.043
Patient perception that pain problem was taken seriously by treating physician				
Overall	69	1.269	0.467-3.451	0.640
CP→OUD group	53	1.021	0.313-3.331	0.973
OUD→CP group	16	3.000	0.361-24.919	0.309

4.5.3 Psychiatric morbidity

The impact of psychiatric morbidity was examined using the GHQ-28 (psychiatric 'caseness' and four subscales) and the SPDQ (social phobia).

Table 4.18a: *Univariate predictors (psychiatric morbidity) of initiation of illicit opioid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Psychiatric 'caseness' (GHQ-28)				
Overall	91	5.637	2.137-14.869	<0.001
CP→OUD group	67	6.560	2.190-19.648	0.001
OUD→CP group	24	4.500	0.395-51.298	0.226
Severe depression (GHQ-28 subscale)				
Overall	104	2.544	1.137-5.688	0.023
CP→OUD group	75	2.667	1.005-7.077	0.049
OUD→CP group	29	2.567	0.562-11.720	0.224
Anxiety/insomnia (GHQ-28 subscale)				
Overall	104	3.006	1.346-6.711	0.007
CP→OUD group	75	6.250	2.248-17.375	<0.001
OUD→CP group	29	0.571	0.123-2.658	0.476
Somatic symptoms (GHQ-28 subscale)				
Overall	104	2.146	0.928-4.965	0.074
CP→OUD group	75	5.600	1.813-17.293	0.003
OUD→CP group	29	0.286	0.059-1.375	0.118
Social dysfunction (GHQ-28 subscale)				
Overall	104	4.853	1.866-12.620	0.001
CP→OUD group	75	9.091	2.399-34.455	0.001
OUD→CP group	29	1.750	0.376-8.140	0.476
Social phobia (SPDQ)				
Overall	96	1.611	0.709-3.664	0.255
CP→OUD group	72	2.020	0.745-5.478	0.167
OUD→CP group	24	0.914	0.174-4.811	0.916

NOTE: Presence of each of the above conditions was determined by applying recommended thresholds to the scales to create binary variables indicating whether or not patients approximated clinically-diagnostic status.

Table 4.18b: *Univariate predictors (psychiatric morbidity) of continued illicit opioid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Psychiatric 'caseness' (GHQ-28)				
Overall	83	2.226	0.888-5.583	0.088
CP→OUD group	53	1.247	0.414-3.754	0.695
OUD→CP group	30	8.000	1.252-51.137	0.028
Severe depression (GHQ-28 subscale)				
Overall	96	1.722	0.717-4.133	0.224
CP→OUD group	63	1.214	0.436-3.382	0.710
OUD→CP group	33	6.769	0.729-62.861	0.093
Anxiety/insomnia (GHQ-28 subscale)				
Overall	96	1.020	0.432-2.411	0.964
CP→OUD group	63	0.662	0.235-1.864	0.435
OUD→CP group	33	2.962	0.507-17.295	0.228
Somatic symptoms (GHQ-28 subscale)				
Overall	96	1.733	0.709-4.236	0.228
CP→OUD group	63	2.082	0.705-6.143	0.184
OUD→CP group	33	1.200	0.239-6.025	0.825
Social dysfunction (GHQ-28 subscale)				
Overall	96	2.196	0.857-5.627	0.101
CP→OUD group	63	1.647	0.528-5.131	0.390
OUD→CP group	33	3.500	0.600-20.414	0.164
Social phobia (SPDQ)				
Overall	88	1.504	0.609-3.716	0.376
CP→OUD group	57	0.754	0.251-2.263	0.614
OUD→CP group	31	5.625	0.915-34.572	0.062

NOTE: Presence of each of the above conditions was determined by applying recommended thresholds to the scales to create binary variables indicating whether or not patients approximated clinically-diagnostic status.

Table 4.19a: *Univariate predictors (psychiatric morbidity) of initiation of nonmedical benzodiazepine use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Psychiatric 'caseness' (GHQ-28)				
Overall	73	10.045	3.193-31.607	<0.001
CP→OUD group	58	10.500	2.800-39.374	<0.001
OUD→CP group	15	13.500	0.878-207.624	0.062
Severe depression (GHQ-28 subscale)				
Overall	83	3.833	1.348-10.899	0.012
CP→OUD group	64	3.652	1.051-12.686	0.041
OUD→CP group	19	5.250	0.698-39.476	0.107
Anxiety/insomnia (GHQ-28 subscale)				
Overall	83	2.995	1.154-7.775	0.024
CP→OUD group	64	7.456	1.905-29.186	0.004
OUD→CP group	19	0.750	0.115-4.898	0.764
Somatic symptoms (GHQ-28 subscale)				
Overall	83	4.138	1.375-12.456	0.012
CP→OUD group	64	7.500	1.550-36.296	0.012
OUD→CP group	19	2.000	0.321-12.840	0.465
Social dysfunction (GHQ-28 subscale)				
Overall	83	4.637	1.417-15.171	0.011
CP→OUD group	64	6.840	1.412-33.141	0.017
OUD→CP group	19	2.333	0.310-17.545	0.410
Social phobia (SPDQ)				
Overall	76	2.249	0.799-6.329	0.125
CP→OUD group	60	4.174	1.051-16.571	0.042
OUD→CP group	16	0.438	0.035-5.395	0.519

NOTE: Presence of each of the above conditions was determined by applying recommended thresholds to the scales to create binary variables indicating whether or not patients approximated clinically-diagnostic status.

Table 4.19b: *Univariate predictors (psychiatric morbidity) of continued nonmedical benzodiazepine use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Psychiatric 'caseness' (GHQ-28)				
Overall	100	2.048	0.887-4.725	0.093
CP→OUD group	62	1.812	0.645-5.093	0.259
OUD→CP group	38	2.381	0.550-10.315	0.246
Severe depression (GHQ-28 subscale)				
Overall	116	0.989	0.458-2.136	0.978
CP→OUD group	74	0.833	0.319-2.179	0.710
OUD→CP group	42	1.333	0.366-4.853	0.663
Anxiety/insomnia (GHQ-28 subscale)				
Overall	116	1.762	0.799-3.883	0.160
CP→OUD group	74	2.250	0.822-6.158	0.114
OUD→CP group	42	1.156	0.317-4.211	0.827
Somatic symptoms (GHQ-28 subscale)				
Overall	116	1.355	0.605-3.032	0.460
CP→OUD group	74	1.607	0.585-4.419	0.358
OUD→CP group	42	1.000	0.262-3.815	>0.999
Social dysfunction (GHQ-28 subscale)				
Overall	116	0.692	0.312-1.535	0.365
CP→OUD group	74	0.630	0.223-1.780	0.383
OUD→CP group	42	0.750	0.207-2.718	0.661
Social phobia (SPDQ)				
Overall	107	1.698	0.757-3.807	0.199
CP→OUD group	69	1.038	0.382-2.825	0.941
OUD→CP group	38	3.778	0.889-16.054	0.072

NOTE: Presence of each of the above conditions was determined by applying recommended thresholds to the scales to create binary variables indicating whether or not patients approximated clinically-diagnostic status.

Table 4.20a: *Univariate predictors (psychiatric morbidity) of initiation of illicit cannabinoid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Psychiatric 'caseness' (GHQ-28)				
Overall	96	0.979	0.437-2.195	0.959
CP→OUD group	60	3.571	1.011-12.610	0.048
OUD→CP group	36	2.500	0.256-24.375	0.430
Severe depression (GHQ-28 subscale)				
Overall	101	1.179	0.534-2.603	0.684
CP→OUD group	63	1.526	0.490-4.747	0.466
OUD→CP group	38	1.885	0.446-7.969	0.389
Anxiety/insomnia (GHQ-28 subscale)				
Overall	101	1.213	0.542-2.715	0.638
CP→OUD group	63	2.143	0.606-7.573	0.237
OUD→CP group	38	1.885	0.446-7.969	0.389
Somatic symptoms (GHQ-28 subscale)				
Overall	101	0.677	0.299-1.534	0.350
CP→OUD group	63	1.161	0.346-3.901	0.809
OUD→CP group	38	0.774	0.190-3.159	0.721
Social dysfunction (GHQ-28 subscale)				
Overall	101	0.519	0.226-1.191	0.122
CP→OUD group	63	1.031	0.304-3.501	0.961
OUD→CP group	38	0.457	0.108-1.937	0.288
Social phobia (SPDQ)				
Overall	101	0.524	0.236-1.163	0.112
CP→OUD group	65	0.733	0.245-2.191	0.579
OUD→CP group	36	0.675	0.160-2.851	0.593

NOTE: Presence of each of the above conditions was determined by applying recommended thresholds to the scales to create binary variables indicating whether or not patients approximated clinically-diagnostic status.

Table 4.20b: *Univariate predictors (psychiatric morbidity) of continued illicit cannabinoid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Psychiatric 'caseness' (GHQ-28)				
Overall	77	1.136	0.506-2.552	0.757
CP→OUD group	60	0.495	0.121-2.019	0.326
OUD→CP group	17	8.750	0.737-103.824	0.086
Severe depression (GHQ-28 subscale)				
Overall	86	1.010	0.406-2.512	0.983
CP→OUD group	63	0.493	0.159-1.525	0.219
OUD→CP group	23	4.500	0.670-30.230	0.122
Anxiety/insomnia (GHQ-28 subscale)				
Overall	86	0.609	0.245-1.514	0.286
CP→OUD group	63	0.588	0.191-1.814	0.356
OUD→CP group	23	0.595	0.114-3.102	0.538
Somatic symptoms (GHQ-28 subscale)				
Overall	86	1.316	0.493-3.515	0.584
CP→OUD group	63	0.837	0.269-2.609	0.760
OUD→CP group	23	3.333	0.292-38.082	0.333
Social dysfunction (GHQ-28 subscale)				
Overall	86	0.875	0.331-2.318	0.789
CP→OUD group	63	0.563	0.176-1.795	0.331
OUD→CP group	23	2.250	0.321-15.756	0.414
Social phobia 'caseness' (SPDQ)				
Overall	82	1.412	0.521-3.825	0.498
CP→OUD group	64	1.067	0.337-3.378	0.913
OUD→CP group	18	4.000	0.500-31.981	0.191

NOTE: Presence of each of the above conditions was determined by applying recommended thresholds to the scales to create binary variables indicating whether or not patients approximated clinically-diagnostic status.

4.5.4 Treatment characteristics

The impact of changes in opioid treatment during the follow-up period was examined. This focused on the change in opioid analgesic dose, ORT dose and total opioid dose (analgesics plus ORT drugs).

Table 4.21a: *Univariate predictors (treatment characteristics) of initiation of illicit opioid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Increased morphine-equivalent opioid analgesic dose				
Overall	34	2.500	0.529-11.813	0.247
CP→OUD group	21	1.875	0.266-13.202	0.528
OUD→CP group	13	4.000	0.299-53.468	0.295
Increased morphine-equivalent opioid replacement therapy (ORT) dose				
Overall	110	1.909	0.892-4.085	0.096
CP→OUD group	80	3.038	1.217-7.587	0.017
OUD→CP group	30	0.583	0.137-2.481	0.466
Increased total opioid dose (analgesic opioid + ORT morphine-equivalent doses)				
Overall	110	1.761	0.824-3.761	0.144
CP→OUD group	80	2.450	0.993-6.047	0.052
OUD→CP group	30	0.750	0.177-3.173	0.696

NOTE: Binary predictor variables were established based on whether or not opioid dose increased during the follow-up period.

Table 4.21b: *Univariate predictors (treatment characteristics) of continued illicit opioid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Increased morphine-equivalent opioid analgesic dose				
Overall	33	0.526	0.096-2.882	0.459
CP→OUD group	16	0.333	0.032-3.515	0.361
OUD→CP group	17	0.800	0.056-11.504	0.870
Increased morphine-equivalent opioid replacement therapy (ORT) dose				
Overall	102	0.792	0.351-1.788	0.575
CP→OUD group	68	1.190	0.449-3.157	0.726
OUD→CP group	34	0.224	0.039-1.303	0.096
Increased total opioid dose (analgesic opioid + ORT morphine-equivalent doses)				
Overall	102	0.951	0.422-2.144	0.903
CP→OUD group	68	1.312	0.495-3.481	0.585
OUD→CP group	34	0.310	0.053-1.793	0.191

NOTE: Binary predictor variables were established based on whether or not opioid dose increased during the follow-up period.

Table 4.22a: *Univariate predictors (treatment characteristics) of initiation of nonmedical benzodiazepine use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Increased morphine-equivalent opioid analgesic dose				
Overall	24	0.636	0.099-4.087	0.634
CP→OUD group	16	0.500	0.050-4.978	0.554
OUD→CP group	8	1.000	0.041-24.547	>0.999
Increased morphine-equivalent opioid replacement therapy (ORT) dose				
Overall	87	1.029	0.424-2.494	0.950
CP→OUD group	66	1.275	0.449-3.620	0.648
OUD→CP group	21	0.530	0.100-3.273	0.530
Increased total opioid dose (analgesic opioid + ORT morphine-equivalent doses)				
Overall	87	1.674	0.686-4.083	0.258
CP→OUD group	66	1.667	0.586-4.70	0.338
OUD→CP group	21	1.750	0.306-10.022	0.530

NOTE: Binary predictor variables were established based on whether or not opioid dose increased during the follow-up period.

Table 4.22b: *Univariate predictors (treatment characteristics) of continued nonmedical benzodiazepine use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Increased morphine-equivalent opioid analgesic dose				
Overall	42	0.857	0.205-3.589	0.833
CP→OUD group	21	0.500	0.073-3.435	0.481
OUD→CP group	21	1.818	0.160-20.714	0.630
Increased morphine-equivalent opioid replacement therapy (ORT) dose				
Overall	124	2.283	1.078-4.837	0.031
CP→OUD group	82	1.930	0.777-4.796	0.157
OUD→CP group	42	3.240	0.849-12.360	0.085
Increased total opioid dose (analgesic opioid + ORT morphine-equivalent doses)				
Overall	124	2.647	1.242-5.643	0.012
CP→OUD group	82	2.045	0.820-5.104	0.125
OUD→CP group	42	4.500	1.147-17.648	0.031

NOTE: Binary predictor variables were established based on whether or not opioid dose increased during the follow-up period.

Table 4.23a: *Univariate predictors (treatment characteristics) of initiation of illicit cannabinoid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Increased morphine-equivalent opioid analgesic dose				
Overall	34	1.309	0.310-5.533	0.714
CP→OUD group	12	0.667	0.032-14.033	0.794
OUD→CP group	22	1.100	0.149-8.125	0.926
Increased morphine-equivalent opioid replacement therapy (ORT) dose				
Overall	106	3.142	1.415-6.976	0.005
CP→OUD group	68	3.561	1.165-10.890	0.026
OUD→CP group	38	12.500	1.397-111.836	0.024
Increased total opioid dose (analgesic opioid + ORT morphine-equivalent doses)				
Overall	106	2.874	1.299-6.355	0.009
CP→OUD group	68	3.561	1.165-10.890	0.026
OUD→CP group	38	10.769	1.205-96.212	0.033

NOTE: Binary predictor variables were established based on whether or not opioid dose increased during the follow-up period.

Table 4.23b: *Univariate predictors (treatment characteristics) of continued illicit cannabinoid use between study inception and 5-year follow-up.*

	n	OR	95% CI	*p*
Increased morphine-equivalent opioid analgesic dose				
Overall	27	0.700	0.145-3.370	0.656
CP→OUD group	20	0.556	0.080-3.858	0.552
OUD→CP group	7	2.000	0.090-44.350	0.661
Increased morphine-equivalent opioid replacement therapy (ORT) dose				
Overall	92	2.182	0.886-5.371	0.090
CP→OUD group	67	1.667	0.561-4.949	0.358
OUD→CP group	25	3.556	0.651-19.412	0.143
Increased total opioid dose (analgesic opioid + ORT morphine-equivalent doses)				
Overall	92	3.304	1.315-8.305	0.011
CP→OUD group	67	2.481	0.819-7.516	0.108
OUD→CP group	25	6.667	1.145-38.833	0.035

NOTE: Binary predictor variables were established based on whether or not opioid dose increased during the follow-up period.

4.5.5 Summary of section findings: Clinical predictors of initiation and continuation of illicit substance use during the follow-up period

The sociodemographic characteristics were broadly similar in both groups. In the CP→OUD group, increasing age was protective of continued nonmedical benzodiazepine use. In the OUD→CP group, male gender was protective of initiation of cannabinoid use and living alone was protective of continued nonmedical benzodiazepine use.

No physical health characteristics were associated with initiation or continuation of illicit opioid use in the OUD→ CP group. In the CP→OUD group, increasing MAP Physical Health subscale scores and increasing pain intensity were risk factors for initiation of illicit opioid use, whilst patient perceptions of their pain problem having been taken seriously by the treating physician was a protective factor. Sleep interference of pain in this group was a risk factor for continuation of illicit opioid use. No physical health characteristics were associated with initiation or continuation of nonmedical benzodiazepine use in the CP→OUD group. In the OUD→ CP group, increasing duration of pain was protective of continuation of nonmedical benzodiazepine use. Patient perceptions of their pain problem having been taken seriously by the treating physician were protective of initiation of cannabinoid use in the CP→OUD group and pain interference on daily activities was a risk factor for continuation of illicit cannabinoid use in the OUD→CP group.

A number of psychiatric characteristics were associated with risk of initiation of illicit opioid use and all related to the CP→OUD group only. Elevated risk in this group was associated with psychiatric 'caseness' (OR=6.560); severe depression (OR=2.667); anxiety/insomnia (OR=6.250); somatic symptoms (OR=5.600); and social dysfunction (OR=9.091). Conversely, risk for continuation of illicit opioid use was associated with psychiatric 'caseness' in the OUD→CP group (OR=1.247). Similar to the findings associated with initiation of illicit opioid use, all findings associated with initiation of nonmedical benzodiazepine use were reported for the CP→OUD group only. Elevated risk in this group was associated with psychiatric 'caseness' (OR=10.500); severe depression (OR=3.652); anxiety/insomnia (OR=7.456); somatic symptoms (OR=7.500); social dysfunction (OR=6.840); and social phobia (OR=4.174). There were no significant associations with continuation of nonmedical benzodiazepine use. Psychiatric 'caseness' was associated with elevated risk of initiation of illicit cannabinoid use in the CP→OUD group only (OR=3.571). There were no other significant associations with initiation or continuation of illicit cannabinoid use during the follow-up period.

Increased ORT dose during the follow-up period was significantly associated with an elevated risk of initiation of illicit opioid use in the CP→OUD group during the same period (OR=3.038).

Conversely, increased total opioid dose (analgesics plus ORT drugs) during the follow-up period was significantly associated with an elevated risk of continuation of nonmedical benzodiazepine use in the OUD→CP group during the same period (OR=3.038). In both groups elevated risk of initiation of illicit cannabinoid use was associated with increased ORT dose (OR in CP→OUD group = 3.561; OR in OUD→CP group = 12.500) and total opioid dose (OR in CP→OUD group = 3.561; OR in OUD→CP group = 10.769). Elevated risk of continuation of illicit cannabinoid use was associated with an increased total opioid dose in the OUD→CP group only (OR=6.667).

4.6 Summary of chapter findings

The first objective was to establish groups based on the patient-attributed causal relationship between chronic pain (CP) and opioid use disorder (OUD). Just over two thirds of the cohort (69%, n=174) reported that CP had caused OUD [the ***CP→OUD group***] whilst the remainder (31%, n=78) reported that OUD had caused CP [the ***OUD→CP group***].

The second objective was to evaluate whether these two groups presented as similar or distinct clinical populations, in respect of sociodemographic and clinical profiles. Both groups were very similar concerning sociodemographic profiles and home and family characteristics. The CP→OUD group was associated with a significantly higher duration of pain at study inception and reported a significantly higher mean pain intensity score. More than three quarters of both groups reported pain interference on daily activities and on sleep quality. A significantly smaller proportion of the OUD→CP group was reported to be stabilised in ORT treatment and a significantly higher proportion of this group reported illicit use of any substances, in particular, methadone, analgesic opioids and cannabinoids. This group was also associated with significantly more intravenous drug use and a significantly higher health risk due to IV use. The OUD→CP group was associated with a statistically significantly higher mean score on the MAP physical health subscale, indicating poorer physical health. Furthermore, this group was associated with a higher mean number of nights spent in general hospitals. Psychiatric 'caseness' was indicated in a significantly higher proportion of the OUD→CP group. Furthermore, a significantly higher proportion of this group was associated, specifically, with social phobia and greater symptom severity on several GHQ-28 subscales (social dysfunction, somatic symptoms and anxiety/insomnia) and CORE subscales (problems/symptoms, life functioning and risk/harm). Of those that were admitted to psychiatric hospitals , the OUD→CP group spent a significantly higher mean number of nights in inpatient facilities.

The third objective was to examine whether these two groups were in receipt of similar treatment for chronic pain (focusing specifically on opioids) and opioid dependence (including

benzodiazepine, a common adjunct in ORT), or if treatment differed between groups at both study inception and during the follow-up period. There were no significant group differences concerning the proportion in receipt of opioid analgesics at study inception; however, of those in receipt of prescribed opioid analgesics, the CP→OUD group was in receipt of a significantly higher morphine-equivalent daily dose. Despite this finding, there was no significant group difference concerning patient satisfaction with treatment for pain problems. There were no significant group differences concerning methadone dose, receipt of benzodiazepines or diazepam-equivalent daily benzodiazepine dose at study inception; however, the OUD→CP group was significantly less satisfied with ORT treatment than the CP→OUD group. There was no significant group difference associated with total opioid dose (i.e. opioid analgesic dose plus ORT dose). There were no significant group differences concerning the proportion in receipt of increasing doses of opioid medication during the follow-up period; around a third of those prescribed opioid analgesics in each group was in receipt of increasing doses and just over half of each group was in receipt of increasing doses of ORT drugs.

The fourth objective was to evaluate the predictive capacity of clinical and treatment characteristics on long-term illicit or nonmedical substance use. Poorer physical health and increasing pain intensity at study inception were predictive of initiation of opioid misuse in the CP→OUD group only, whilst patient perceptions of their pain problem having been taken seriously by the treating physician were protective in this group. Sleep interference at study inception was predictive of continuation of illicit opioid use in this group. Increasing duration of pain at study inception was protective of continuation of nonmedical benzodiazepine use in the OUD→CP group only. Similar to the finding associated with illicit opioid use, in the CP→OUD group, patient perceptions of their pain problem having been taken seriously by the treating physician were protective of initiation of cannabinoid use (OR=0.153). Pain interference on daily activities at study inception was predictive of continuation of illicit cannabinoid use in the OUD→CP group only. A number of psychiatric characteristics were predictive of initiation of illicit opioid, benzodiazepine and cannabinoid use in the CP→OUD group only. Conversely, risk for continuation of illicit opioid use was associated with psychiatric 'caseness' in the OUD→CP group. Increased therapeutic opioid dose during the follow-up period was predictive of initiation of illicit opioid use in the CP→OUD group during the same period. Increased dose was predictive of initiation of nonmedical benzodiazepine use and continuation of illicit cannabinoid use in the OUD→CP group and predictive of initiation of illicit cannabinoid use in both groups.

Chapter 5

Incidence of iatrogenic opioid dependence or abuse in patients exposed to opioid analgesic treatment: A systematic review and meta-analysis

5.1 Introduction

5.1.1 Rationale

The risk of physical dependence and abuse associated with opioids is a major clinical concern that may deter adequate analgesic prescribing for patients whose previous treatment regimens have proven unsuccessful (Jamison et al., 2011). To ensure that patients are not denied treatment unnecessarily, there is a need for quantification of the risk of opioid dependence or abuse as a consequence of analgesic treatment. Several reviews have examined the relationship between opioid analgesic prescribing and opioid misuse; however, many examined prevalence (existing cases) – rather than incidence (new cases) – and, in consequence, were unable to conclude that dependence or abuse was a function of opioid analgesic exposure. Within this domain of study there are several terms that are used in an ill-defined way or even used interchangeably. Many studies have used the wider, and relatively ambiguous, outcomes of 'addiction', 'drug misuse' or 'aberrant drug-related behaviour' – not necessarily indicating problematic substance use, since these concepts include recreational use and other forms of non-problematic use. Furthermore, since most studies included in these reviews were unable to control for pre-existing opioid misuse, findings may reflect prevalence – rather than incidence – and, therefore, may not indicate an iatrogenic syndrome.

Littlejohn et al. (2004) undertook a review of the literature which generated a wide range of prevalence rates and they did not attempt to generate pooled estimates. They did not focus solely on incidence and, therefore, could not demonstrate that drug use was a function of chronic opioid analgesic therapy (COAT). Noble *et al.* (2010) intended to generate pooled estimates but, due to restrictive inclusion criteria concerning study design, they were unable to identify sufficient homogenous studies. Whilst Fishbain (2008) undertook a relatively robust and well-documented review it responded to a different question to that of the current review – it focused on abuse/ADRB rather than on a clinical dependence or abuse disorder and, furthermore, it is now outdated. Minozzi *et al.* (2013a) did focus exclusively on dependence and

differentiated between incidence and prevalence; however, a failure to develop and adhere to narrowly-defined inclusion criteria resulted in substantial heterogeneity across included studies and, consequently, an inability to established pooled estimates. Vowles *et al.* (2015) examined current prevalence rates of opioid misuse and addiction. This again, is a slightly different question to that of the current review since there was no focus specifically on clinical disorders. Furthermore, prevalence rates do not indicate an iatrogenic syndrome since there is no evidence to suggest that opioid prescribing preceded addiction.

Whilst the physiological characteristics of acute dependence are anticipated following prolonged exposure to opioids, clinical diagnoses of opioid dependence or abuse disorders are not. Acute tolerance is demonstrated to occur several minutes or hours following exposure (e.g. Matthews, *et al.*, 2008); however, dependence associated with prolonged exposure has not be characterised. Some studies have suggested that the proposed 7 days (Glatt, 1974) has not been challenged adequately and remains a valid threshold (e.g. Cowan, 2003) whilst some studies have used a more cautious approach to ensure that there is no controversy – for example, 2 weeks (Eddy, 1959), 1 month (Fishbain, 2008) or 3 months (Edlund, 2014). The development of addiction and abuse is influenced by numerous factors and, as such, cannot be considered to be a direct function solely of opioid prescribing. A precursor to disentangling the role of opioid prescribing in the development of addiction is to, first, examine the relationship between opioid prescribing and the development of an iatrogenic clinical opioid dependence or abuse disorder.

5.1.2 Objective

The primary objective of the current review was to generate a pooled estimate of the incidence of iatrogenic, clinically-diagnostic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy. It was hoped that data concerning dependence and abuse would be provided independently; however, it was anticipated that this distinction would not be made in studies. In the absence of distinct data for these two disorders, it was decided that data for these disorders would be pooled to provide an indication of a clinical dependence/abuse disorder. Should substantial heterogeneity be identified, it was proposed that sensitivity analyses would be undertaken in an effort to explain variance in study effects.

Assuming the emergence of sufficient data from relatively homogenous studies, the secondary objective was to undertake subgroup analyses for characteristics associated with opioid analgesic prescribing and opioid dependence. Proposed subgroup analyses are discussed further in the Methods section.

The established PICOS framework (**P**opulation, **I**nterventions, **C**omparators, **O**utcomes and **S**tudy design) was used to design the current review and to develop an appropriate search strategy. The findings are reported in accordance with the recommendations set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher, 2009).

5.2 Methods

5.2.1 Protocol and registration

The review protocol was registered on PROSPERO which is an international database of prospectively registered systematic reviews in health and other related domains of study. PROSPERO is produced by the Centre for Reviews and Dissemination (CRD, University of York) and is funded by the National Institute for Health Research (NIHR). A copy of the PROSPERO registration can be found in Appendix III. The protocol registration number is CRD42017058445 and it can be accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017058445.

5.2.2 Eligibility criteria

Searches were undertaken on 1 April 2017 and no date restrictions were applied; eligible articles were restricted to those written in the English language.

Populations were included if they were human and were in receipt of prescribed opioids for the treatment of pain. Studies focussing on opioid exposure in healthy volunteers or opioid replacement therapy (ORT) for the treatment of opioid dependence were excluded.

Interventions took the form of opioid analgesic treatment for a sufficient length of time for dependence to develop potentially. This is, of course, dependent upon a number of complex drug- and patient-related characteristics and the time between exposure and the development of dependence has not yet been characterised in humans. Data were extracted from all studies where participants were exposed to opioid analgesics for 7 days or more and sensitivity analyses were undertaken based on the conservative exposure threshold of 3 months.

Comparator populations were included if treated with a different opioid analgesic than the target group (i.e. included as a second target cohort) but not if they were treated with a non-opioid analgesic. Where studies examined more than one group treated with opioid analgesics, the total population and event rates were summed and included in the principal analysis. Group-level data were also extracted with the aim of undertaking subgroup analyses (active ingredient and strong/weak opioids) where sufficient data and study homogeneity permitted these subgroup analyses.

Outcomes comprised incidence rates from articles that specified a clinical diagnosis of opioid dependence or abuse disorder (in accordance with DSM/ICD criteria or through clinician assessment). Studies were excluded if they relied upon patient reports or proxy indicators of opioid misuse since it is impossible to distinguish between a clinical dependence or abuse disorder and the wider concepts associated with 'addiction' using these methods of data collection. Articles using the terms 'addiction', 'misuse' and 'abuse' were included if this represented a clinical diagnosis of opioid dependence or abuse disorder, in accordance with these diagnostic manuals or identified through clinician assessment.

Study design did not preclude inclusion in the current review; however, secondary data were not included to avoid duplication of articles presenting primary data.

5.2.3 Information sources

Electronic searches were undertaken using: Embase; Medline; PubMed; Cinahl Plus; Web of Science and OpenGrey. Searches were run on 1 April 2017 and no date restrictions were applied. A manual search of the references of included publications was also undertaken. In an attempt to avoid publication bias, a broad manual grey literature search was undertaken; this included examination of conference proceedings, technical reports, organisation websites and dissertations. At a later stage, once included articles had been identified, a manual reference search was undertaken of these included articles.

5.2.4 Search

The search term was constructed using the PICOS principles, shown below, and was run in each of the electronic databases. The English language filter was applied in all databases and the participants filter (human only) was applied where available (Embase, Medline and PubMed). Pilot searches were run to ensure optimisation of the search term and target words were identified based on their net contribution to the identification of relevant articles. Perhaps the most obvious target word that is conspicuous by its absence is 'addiction'. It was run in pilot searches but, given that it tended to identify articles focusing on addicted clinical populations (rather than the development of addiction in patients exposed to opioid analgesics), its net gain was insufficient for inclusion in the search term.

Population: pain AND (opioid* OR opiate* OR buprenorphine OR codeine OR diamorphine OR dihydrocodeine OR dipipanone OR fentanyl OR hydromorphone OR meptazinol OR methadone OR morphine OR oxycodone OR papaveretum OR pentazocine OR pethidine OR

	tramadol OR tapentadol OR levorphanol OR oxymorphone OR meperidine OR butorphanol OR opium OR propoxyphene OR alfentanil OR levomethadyl OR sufentanil OR remifentanil OR dextropropoxyphene OR ketobemidone)
Intervention:	prevalence OR incidence OR rate* OR frequenc* OR proportion* OR percent*
Comparators:	Not included in search strategy
Outcomes:	depend* OR toleran* OR withdraw*
Study design:	Not included in search strategy

5.2.5 Study selection

All abstracts of identified studies were examined and those that clearly did not meet inclusion criteria were excluded. The reason for the exclusion of each article was recorded. Remaining articles underwent full text review and the reason for each article excluded at this stage was recorded. A random selection of 25% of included articles was assessed by a second reviewer who was blind to title, author, journal and year of publication.

5.2.6 Data collection process

A data extraction proforma was designed and piloted with 5 of the included articles. Whilst it was evident that there would not be a full complement of data available for subgroup analyses, all items were retained in the proforma for assessment following the extraction of available data from all included articles. Where required, authors were contacted in an effort to seek clarification on the data presented in articles.

5.2.7 Data items

Author(s), title and date;

Study design;

Study objective: this provided a record of whether incidence rates were a primary or secondary objective of each study;

Number recruited and final number included in sample;

Pain type (malignant or non-malignant);

Nature of pain (nociceptive or neuropathic);

Name of opioid analgesic(s): this item was used to identify strong and weak opioids

Length of exposure to opioid analgesic;

Method for diagnosing opioid dependence disorder (DSM, ICD or clinician assessment;

Event rate: this comprised total population under investigation and number of events reported;
Data required for subgroup analyses: event rate (as above) for all subgroups, as described in 'Additional Analyses';
Additional notes: this was a free text box in which explanatory notes or issues for consideration were recorded.

5.2.8 Risk of bias in individual studies

Assessment of risk of bias in individual studies was undertaken at study level, rather than outcome level. Several instruments (including the commonly-used SIGN and CASP tools) underwent pilot testing with a random selection of 25% of included articles, with the aim of identifying tools that best assessed the most important aspects of study quality associated with the common study designs of included articles. The most important criterion, however, was availability of consistent measures which could be used to assess both types of study designs of included articles. In the present study, assessment of risk of bias in individual studies was achieved using instruments designed by the National Institutes of Health (NIH). A copy of the two instruments used in the present review can be found in Appendices I and II, and copies can be located online at:

- Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group (**URL: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after**)
- Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies **(URL: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort**)

These instruments are not intended to be summed to provide a total score, since assigning scores may be considered to be misleading (Greenland, 2001; Higgins *et al.*, 2006)). Instead, these instruments are designed to prompt consideration of the key concepts relating to internal validity and potential risk of bias in individual study designs. As such, study quality was rated as: 'poor'; 'fair'; or 'good'. These results were entered into the review dataset as a moderator variable and used in sensitivity analyses.

5.2.9 Summary measures

The principal measure used in the primary meta-analysis and in subgroup analyses was event rate. This was entered into the software as total population under investigation and number of events identified; the software provided the computed event rate. The raw event rate was

shown in forest plots and reported as percentages in the main body of the text. Percentages were calculated by multiplying the event rate by 100.

5.2.10 Synthesis of results

Pooled incidence estimates were generated using the random effects (DerSimonian-Laird method) model. Individual studies were weighted in accordance with the principle of inverse variance and, since a random effects model was applied, this included between-study variance in addition to within-study variance. The weighted contribution of each study is reflected in its respective symbol size in each forest plot. The decision to use a random effects model was made *a priori* since it was clear that studies would differ on population characteristics such as age distribution, gender distribution, ethnicity, cultural background, socioeconomic status and a range of clinical characteristics. Using the random effects model, the Cochrane *Q* statistic and the I^2 statistic assessed both within-study and between-study heterogeneity. Whilst the pooled estimated effect size shown in fixed and random effects models can be similar, since the random effects model incorporates an estimate of between-study variance it is, therefore, likely to generate wider confidence intervals. Event rates were used in computational models and were converted to percentages for the purpose of meaningful reporting and discussion.

Heterogeneity is a measure of inconsistency in study outcomes across all studies in a meta-analysis. The classical measure of heterogeneity is Cochran's Q statistic; it is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies (with weights being those used in the pooling method) and is distributed as a chi-square statistic (number of studies minus one degree of freedom). In consequence, the power of Cochran's Q varies according to the number of included studies. The I^2 statistic is not, however, dependent upon the number of included studies (100% x (Q-df)/Q). For the reader's interest, several measures of heterogeneity have been reported (Cochran's Q; Tau^2; and I^2); however, the preferred I^2 statistic (Higgins & Thompson, 2002) was discussed in the text. Definitive heterogeneity thresholds can be misleading; however, The Cochrane Handbook (section 9.5.2) provides a guide to interpreting the I^2 statistic and suggests that ≥50% may represent substantial heterogeneity.

5.2.11 Risk of bias across studies

Publication bias indicates that nonsignificant or negative findings are more likely to remain unpublished making it an essential component of systematic reviews and meta-analyses. Publication bias was assessed using the Egger regression intercept and the Begg-Mazumdar rank correlation test. The use of imputational strategies in meta-analyses remains controversial and,

furthermore, is unlikely to alter the conclusions in over 90% of secondary data analyses (Sutton *et al.*, 2000). In consequence, imputational strategies were not used in the current review.

5.2.12 Additional analyses

Sensitivity analyses were undertaken in an effort to explain substantial heterogeneity. These analyses used both subgroup variables (i.e. within-study patient groups, such as gender) and moderator variables (i.e. between-study characteristics, such as study quality). Meta-regression was used in sensitivity analyses to examine heterogeneity and to test the robustness of findings in light of process decisions.

Subgroup analyses were planned based on characteristics associated with pain, opioid analgesic prescribing and vulnerability to opioid dependence. Moderator variables were based on study quality and whether incidence rates were a primary or secondary objective of each of the included studies. Planned subgroups are shown below.

1. Pain characteristics: malignant/non-malignant; and nociceptive/neuropathic.
2. Treatment characteristics: strong/weak opioids (based on definitions provided in the World Health Organization (WHO) Analgesic ladder.
3. Demographic characteristics: gender; age; and ethnicity.
4. Socioeconomic characteristics: marital status; educational attainment; employment status; etc.
5. Clinical characteristics: mood disorders; anxiety disorders; and a history of substance misuse.

Subgroups and moderator variables were entered into a meta-regression model. Much like regression analysis of primary data, where there is a generally-accepted ratio of ten observations to each predictor, meta-regression of less than ten studies per moderator variable is considered to be unreliable. Within the scope of the current review there were insufficient data to undertake meta-regression with more than one subgroup/moderator variable at a time. Meta-regression was undertaken using the DerSimonian-Laird method, also known as the 'method of moments'.

5.3 Results

5.3.1 Study selection

Electronic searches were undertaken on 1 April 2017 and utilised six research databases. ***Table 5.1*** shows the number of hits generated in both electronic and manual searches, and the number of duplicates identified using the appropriate function in Endnote.

Table 5.1: *Number of hits generated by search terms and number of duplicates identified through the electronic function in Endnote*

Research database	Articles retrieved	Number of duplicates	Running total
Embase ‡	1965	n/a	1965
Medline ‡	1007	277	2695
PubMed ‡	1005	760	2940
Cinahl Plus †	401	218	3123
Web of Science †	1707	426	4404
OpenGrey †	3	0	4407
Manual search	76	0	4483
Total	**6164**	**1681**	**4483**

† Filters applied: Language (English).

‡ Filters applied: Language (English); and Participants (Human).

A manual search for duplicates was undertaken and a further 1040 articles were identified, resulting in a total of 3443 articles retained for eligibility review. ***Figure 5.1*** shows the total number of articles that underwent eligibility review and the total number retained for full text review.

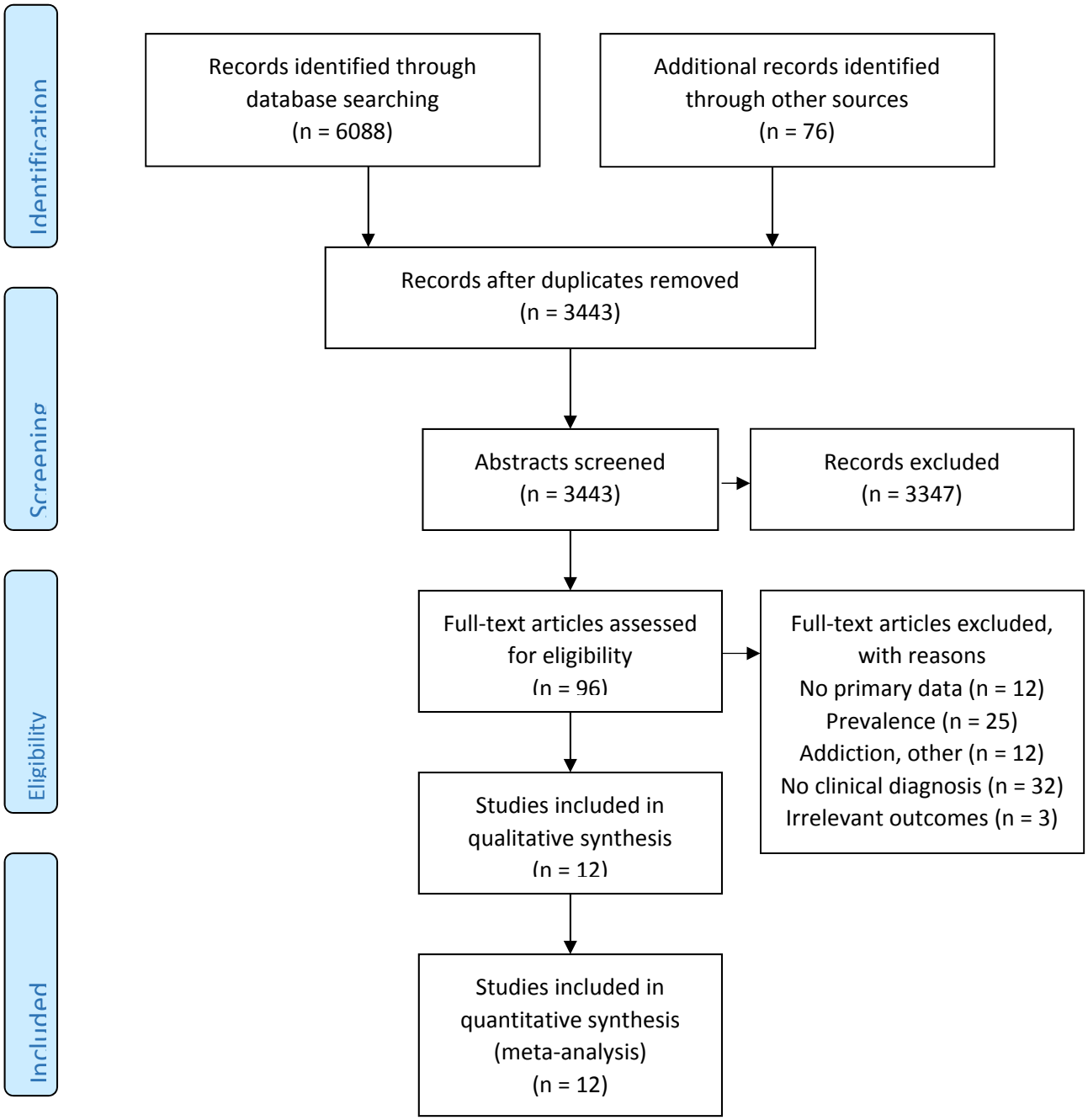


Figure 5.1: *Total number of articles undergoing eligibility review and number of articles retained for inclusion in current review*

Where the same author contributed to more than one included study, articles were reviewed to ensure that participants were not double-counted within the current review. Data were extracted from 12 articles, involving a total of 310,408 participants.

5.3.2 Study characteristics

The characteristics of included studies are shown in ***Table 5.2***. Where incidence of opioid dependence or abuse was not the primary objective or was not the only primary objective, the study design was reported for the method used to obtain incidence data rather than the method used in the overall study. Study design was identified using Agency for Healthcare Research and Quality AHRQ (US DoH) criteria (AHRQ, 2011). One of the included studies (Cowan, 2002) included 16 participants and had an event rate of zero; however, this study was retained in the meta-analysis since CMA has the capacity to apply an adjustment, known as a 'continuity correction', to facilitate inclusion of zero-count studies. A continuity correction involves adding a constant value to each of the cells in the contingency table. In consequence, the event rate for this study was 0.029 (i.e. 2.9%) rather than zero. This does, however, necessarily impact on the confidence interval, widening it substantially, and this can be seen in the main forest plot in ***Figure 5.2***.

Table 5.2: *Characteristics of included studies*

Author (year)	Study design (location)	Malignant/non-malignant pain (N)	Prescription opioid (minimum length of exposure)	Event rate (%)
Adams (2006)	Prospective cohort (USA)	CNCP (6243)	Hydrocodone; tramadol (varied)	5.5
Buse (2012)	Cross-sectional (USA)	CNCP (922)	Any (varied)	16.6
Cepeda (2013)	Prospective cohort (USA)	Mixed (39,367)	Any (12 months)	0.5
Chabal (1997)	Cross-sectional (USA)	CNCP (76)	Any (6 months)	34.2
Cowan (2002)	Pre-post (UK)	CNCP (16)	Any (varied)	2.9
Dersh (2008)	Cross-sectional (USA)	CNCP (1323)	Any (not known)	15.0
Edlund (2007)	Cross-sectional	CNCP (15,160)	Any (3 months)	2.0
Edlund (2010)	Cross-sectional (USA)	CNCP (46,256)	Any (3 months)	3.2
Edlund (2014)	Cross-sectional	CNCP (197,269)	Any (3 months)	0.2
Flemming (2008)	Cross-sectional (USA)	Mixed (904)	Any (varied)	3.4
Huffman (2013)	Pre-post (USA)	CNCP (120)	Any (not known)	32.5
Hylan (2015)	Pre-post (USA)	CNCP (2752)	Any (6 months)	5.7

5.3.3 Risk of bias within studies

As discussed in the Methods section, risk of bias within studies was undertaken at study level, rather than outcome level, and was achieved using instruments designed by the National Institutes of Health (NIH). These instruments generated categorical data pertaining to the

design of individual studies (poor; fair; and good quality). Results are reported in ***Table 5.3*** along with a justification of any studies not identified as 'good quality'.

Table 5.3: *Risk of bias within studies*

Author (year)	Study quality	Justification
Adams (2006)	Fair	Potential statistically significant differences in baseline characteristics were not examined and there are potential confounders associated with physicians making individual treatment decisions as the study progressed.
Buse (2012)	Fair	Potential bias since physicians were responsible for decisions concerning delivery of prescriptions drugs and this was not consistent across participants, and not controlled in the analyses.
Cepeda (2013)	Good	Not applicable.
Chabal (1997)	Fair	Lack of information to enable a good judgement.
Cowan (2002)	Good	Not applicable.
Dersh (2008)	Good	Not applicable.
Edlund (2007)	Good	Not applicable.
Edlund (2010)	Good	Not applicable.
Edlund (2014)	Good	Not applicable.
Flemming (2008)	Good	Not applicable.
Huffman (2013)	Good	Not applicable.
Hylan (2015)	Good	Not applicable.

5.3.4 Synthesis of results

Figure 5.2 shows the overall study effects and summary effect. Individual studies were weighted in accordance with the principle of inverse variance and, since a random effects model was applied, this included between-study variance in addition to within-study variance.

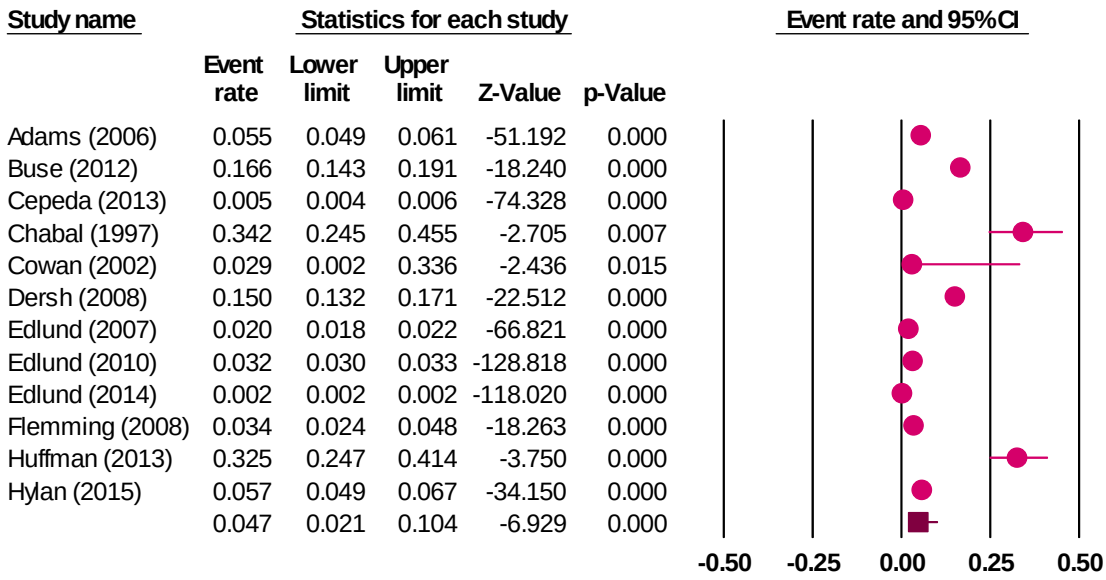


Figure 5.2: *Meta-analysis (random effects model) of overall study findings of the incidence of iatrogenic opioid dependence or abuse. Studies are reported by ascending year of publication.*

The summary effect, the weighted mean of all studies using a random effects model, is shown to be 0.047 (95% CI = 0.021-0.104), indicating that 4.7% of patients prescribed opioid analgesic therapy were associated with *de novo* diagnostic status for opioid dependence or abuse following analgesic treatment. The confidence interval provides a measure of precision and, in the current analysis, it suggests that the 'true' value of the pooled effect size lies within the range 2.1% to 10.4%. The included studies are listed in **Figure 5.3** in chronological order of date of publication and it is shown that there is no pattern associated with findings over time. Substantial heterogeneity was identified in study effects (I^2=99.78) [Q=4973 (df=11); p<0.001; Tau^2=2.146 (SE=1.394; Variance=1.942; Tau=1.465)]. Heterogeneity was anticipated, hence the *a priori* decision to employ the use of a random effects model, and this will be examined further in sensitivity analyses.

5.3.5 Risk of bias across studies

Assessment of risk of publication bias is shown in ***Figure 5.3***. In the absence of heterogeneity and publication bias, 95% of points would lie within the guidelines drawn on the funnel plot.

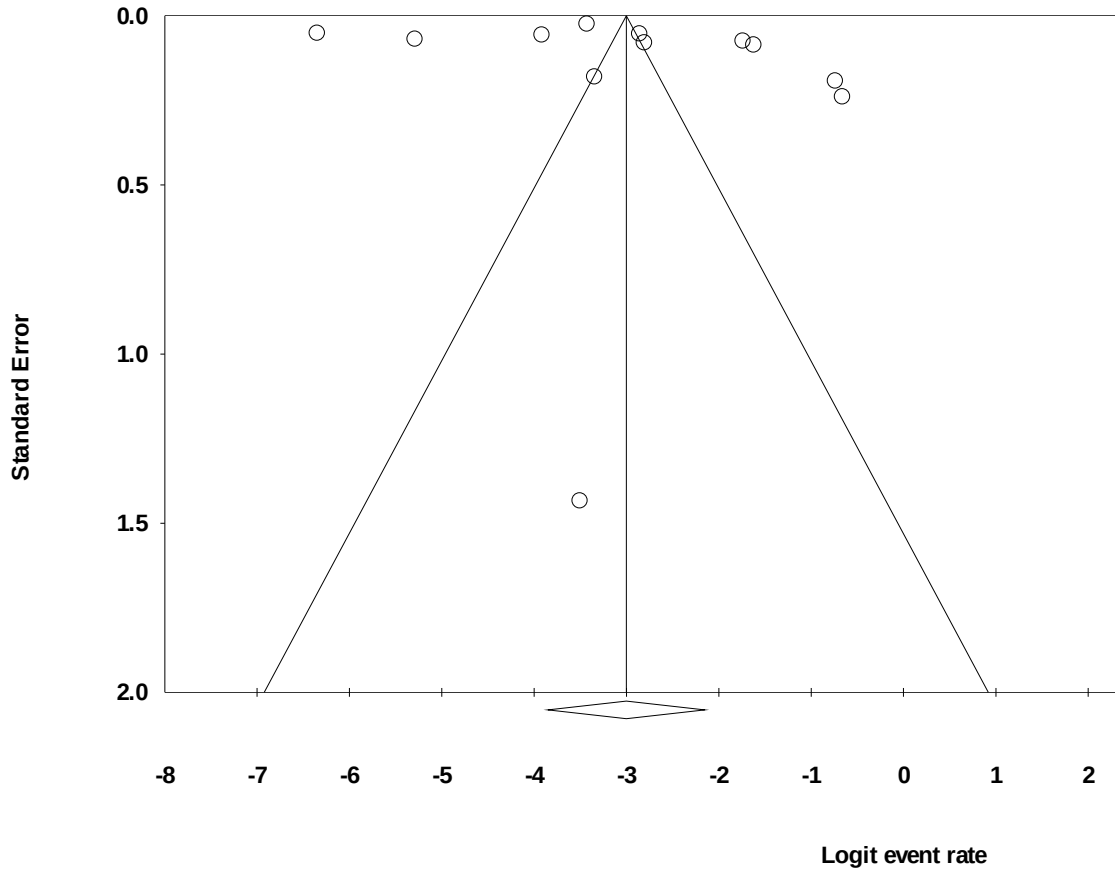


Figure 5.3: *Funnel plot of standard error of study effect by logit event rate*

Figure 5.3 shows a fairly symmetrical distribution; however, many individual studies with relatively high sample sizes (shown towards the top of the plot) fall beyond the anticipated distribution range – both to the left of centre (indicating effect sizes lower than the mean) and to the right of centre (indicating effect sizes higher than the mean). The relatively symmetrical distribution suggests little publication bias, confirmed by the Egger regression intercept (t=0.64; df=10; p=0.536) and the Begg-Mazumdar rank correlation test (Tau=0.15; p=0.493). The previously-reported heterogeneity is, however, evident in the funnel plot and was therefore explored using sensitivity analyses.

5.3.6 Additional analyses

5.3.6.1 Sensitivity analyses for overall heterogeneity of study effects

Given the substantial heterogeneity in study effects (99.78%), a number of sensitivity analyses were computed to assess impact on variance. The forest plots for moderator analyses are shown in ***Figures 5.4 - 5.6***: study design; risk of bias in individual studies; and whether the effect size reported in the current review was a primary or secondary objective of included studies. The forest plots for subgroup analyses are shown in ***Figures 5.7 - 5.10***: diagnostic criteria for identifying dependence or abuse; strength of analgesic opioid; and duration of opioid exposure.

Where significant differences in group summary effects were reported, the appropriate moderator/subgroup variable was entered into a regression model in an effort to explain the overall variance in study effects. Where models significantly explained some of the heterogeneity in study effects, ***Figures Xa*** show a regression of the logit event rate and ***Figures Xb*** show the degree of variance explained by the model.

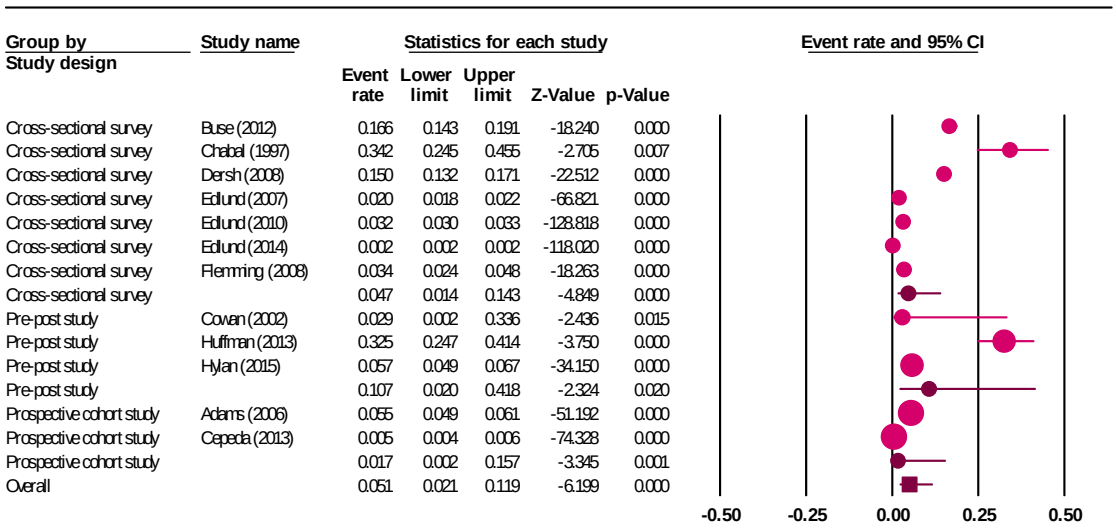


Figure 5.4: *Sensitivity analysis of the incidence of iatrogenic opioid dependence or abuse by study design.*

As ***Figure 5.4*** shows, pooled effect estimates of incidence of iatrogenic opioid dependence or abuse did not differ significantly by study design (p=0.432). Cross-sectional study designs generated a pooled effect of 4.7%; pre-post study designs generated a pooled effect of 10.7%; and prospective cohort study designs generated a pooled effect of 1.7%. Meta-regression generated a non-significant model.

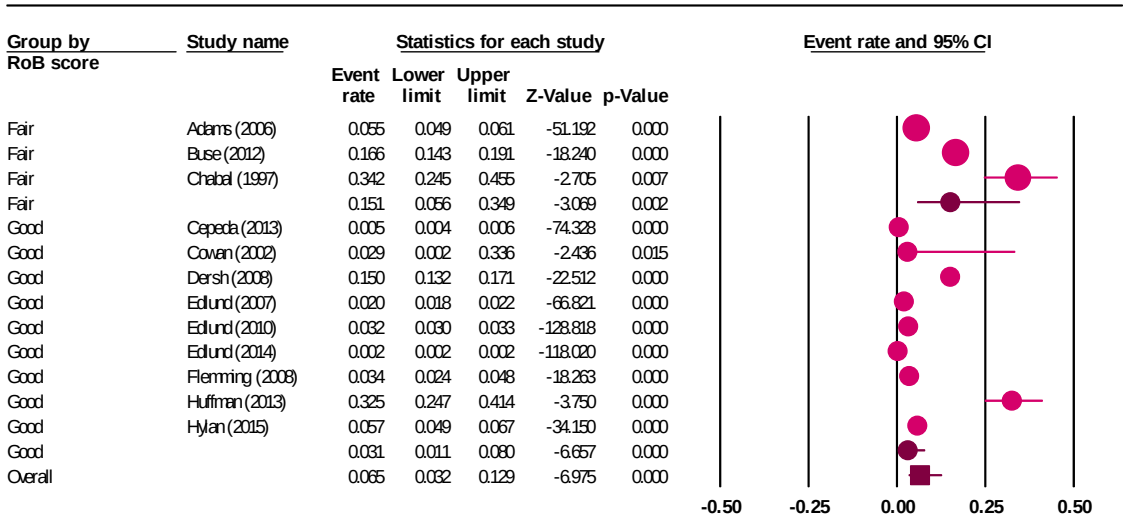


Figure 5.5: *Sensitivity analysis of the incidence of iatrogenic opioid dependence or abuse by quality assessment/risk of bias within studies.*

As ***Figure 5.5*** shows, pooled effect estimates of incidence of iatrogenic opioid dependence or abuse differed significantly by quality assessment/risk of bias within studies (p=0.024). Studies identified as being of 'fair' quality generated a pooled effect of 15.1% whilst studies identified as being of 'good' quality generated a pooled effect of 3.1%. Meta-regression generated a non-significant model.

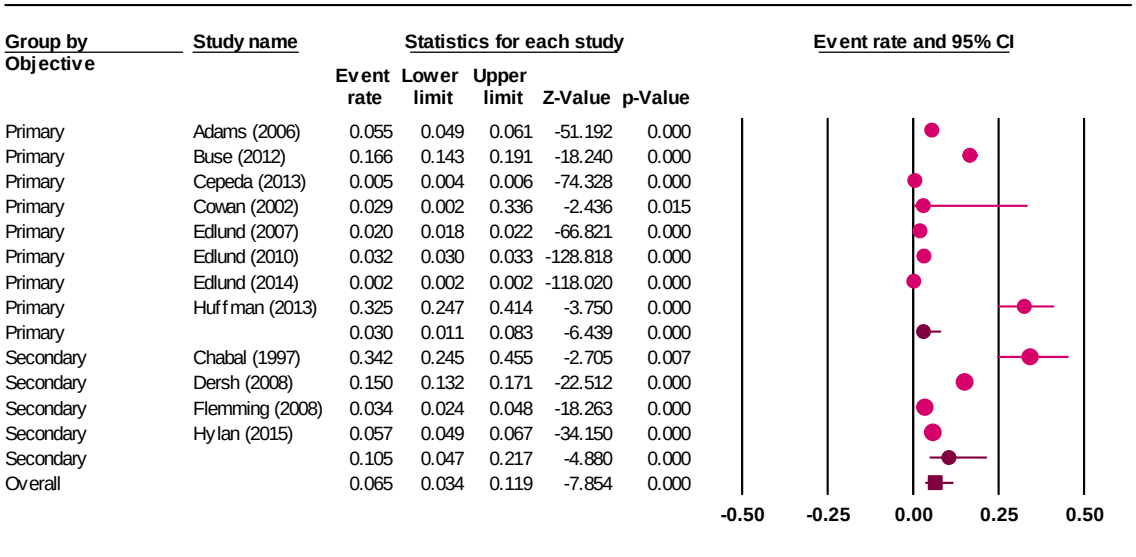


Figure 5.6: *Sensitivity analysis of the incidence of iatrogenic opioid dependence or abuse by whether the effect size reported in the current review was a primary or secondary objective of included studies.*

As ***Figure 5.6*** shows, pooled effect estimates of incidence of iatrogenic opioid dependence or abuse differed by marginal significance by whether the effect size reported in the current review was a primary or secondary objective of included studies (p=0.058). Studies where this was the primary objective generated a pooled effect of 3.0% whilst studies where this was the secondary objective generated a pooled effect of 10.5%. Meta-regression generated a non-significant model.

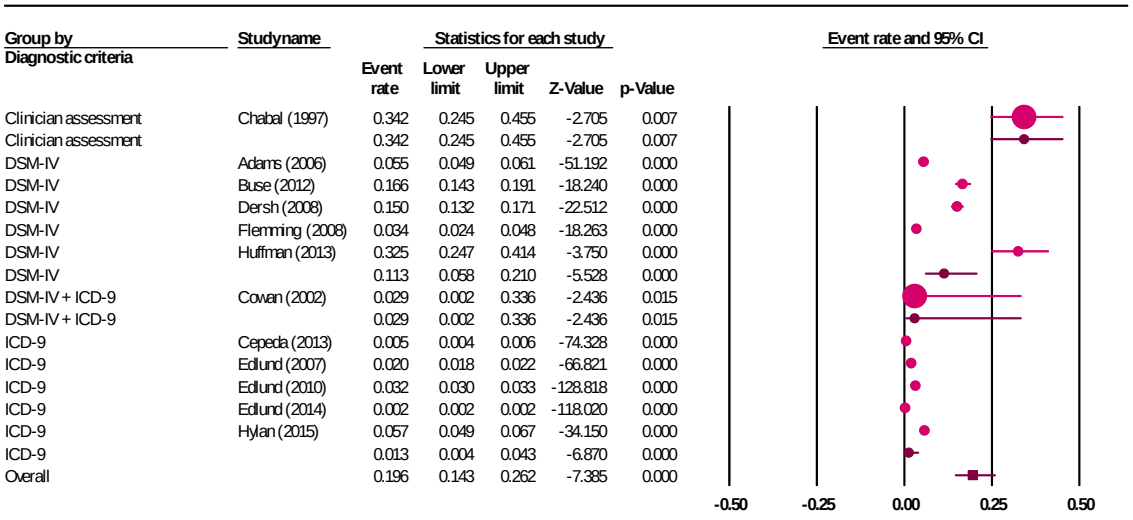


Figure 5.7: *Sensitivity analysis of the incidence of iatrogenic opioid dependence or abuse by diagnostic criteria for identifying dependence or abuse.*

As ***Figure 5.7*** shows, pooled effect estimates of incidence of iatrogenic opioid dependence or abuse differed significantly by diagnostic criteria for identifying dependence or abuse (p<0.001). DSM-IV criteria generated a pooled effect of 11.3%; ICD-9 criteria generated a pooled effect of 1.3%; one study using both DSV-IV and ICD-9 criteria generated an effect of 2.9%; and one study using clinician assessment generated an effect of 34.2%. The analyses were re-run excluding the two single-study groups (the study that used clinician assessment to identify dependence or abuse and the study that used both DSM and ICD criteria). Findings are shown in ***Figure 5.8***.

Group by Diagnostic criteria	Studyname	Event rate	Lower limit	Upper limit	Z-Value	p-Value
DSM-IV	Adams (2006)	0.055	0.049	0.061	-51.192	0.000
DSM-IV	Buse (2012)	0.166	0.143	0.191	-18.240	0.000
DSM-IV	Dersh (2008)	0.150	0.132	0.171	-22.512	0.000
DSM-IV	Flemming (2008)	0.034	0.024	0.048	-18.263	0.000
DSM-IV	Huffman (2013)	0.325	0.247	0.414	-3.750	0.000
DSM-IV		0.113	0.058	0.210	-5.528	0.000
ICD-9	Cepeda (2013)	0.005	0.004	0.006	-74.328	0.000
ICD-9	Edlund (2007)	0.020	0.018	0.022	-66.821	0.000
ICD-9	Edlund (2010)	0.032	0.030	0.033	-128.818	0.000
ICD-9	Edlund (2014)	0.002	0.002	0.002	-118.020	0.000
ICD-9	Hylan (2015)	0.057	0.049	0.067	-34.150	0.000
ICD-9		0.013	0.004	0.043	-6.870	0.000
Overall		0.066	0.037	0.118	-8.246	0.000

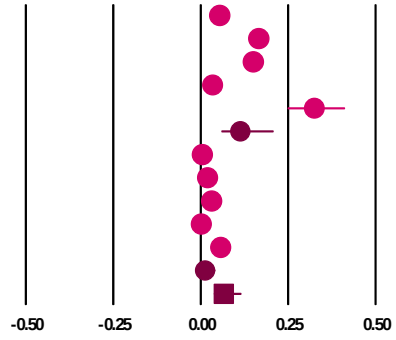


Figure 5.8: *Sensitivity analysis of the incidence of iatrogenic opioid dependence or abuse by DSM-IV and ICD-9 diagnostic criteria for identifying dependence or abuse.*

As ***Figure 5.8*** shows, pooled effect estimates of incidence of iatrogenic opioid dependence or abuse differed significantly by DSM-IV and ICD-9 diagnostic criteria for identifying dependence or abuse (p=0.002). Studies which used ICD-9 criteria generated a pooled effect of 1.3% whilst studies which used DSM-IV criteria generated a pooled effect of 11.3%. The meta-regression model was statistically significant (Q=7.77; df=1; p=0.005); the regression is shown in ***Figure 5.8***a and the results are shown in ***Table 5.4***.

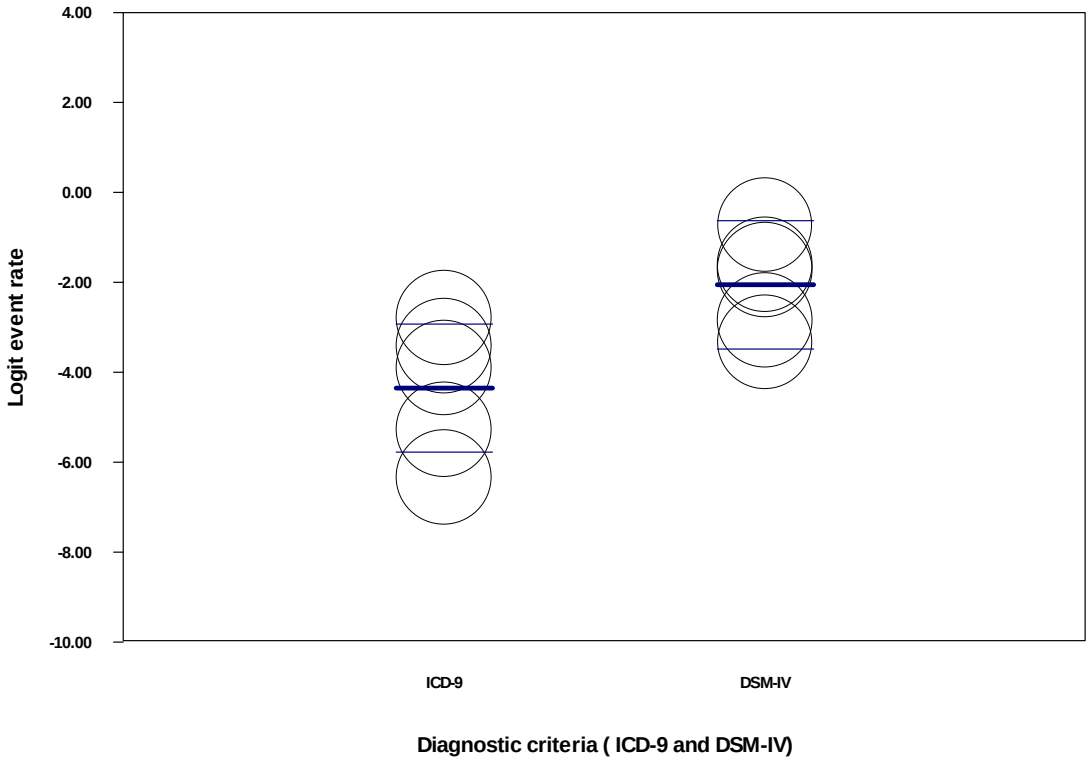
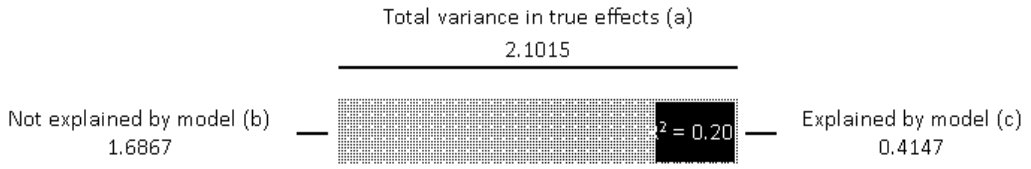


Figure 5.8a: *Regression of logit event rate on diagnostic criteria (ICD-9 and DSM-IV) using a random effects (DerSimonian-Laird) model. Regression line and confidence intervals shown in blue.*

Table 5.4: *Random effects (DerSimonian-Laird) meta-regression of duration of logit event rate on the criteria used to diagnose dependence or abuse (DMS-IV compared with ICD-9) using a Z-distribution*

Covariate	Coefficient	SE	95% lower	95% upper	Z value	p value
Intercept	-4.3506	0.5815	-5.4902	-3.2109	-7.48	<0.0001
DSM-IV	2.2962	0.8240	0.6812	3.9111	2.79	0.0053

The coefficient for the moderator variable is positive, indicating that the use of DSM-IV diagnostic criteria was associated with more than twice the mean effect size of that of the reference category (i.e. ICD-9 criteria). The meta-regression showed that the inclusion of this moderator variable in the regression model explained 20% of the overall variance in study effects (R^2=0.20). ***Figure 5.8b*** shows the R^2 value and an explanation of how this value was ascertained.



$$R^2 = \frac{\text{Explained (c)}}{\text{Total (a)}} = \frac{0.4147}{2.1015} = 0.20$$

(a)	To compute the total variance (about the grand mean) the regression was run with no covariates
(b)	To compute the variance not explained by the model (of all studies about the regression line) the regression was run with the covariate
(c)	The difference between these values gives the variance explained by the model

Figure 5.8b: *R^2 for regression of logit event rate (Z-distribution) on diagnostic criteria (ICD-9 and DSM-IV) using a random effects (DerSimonian-Laird) model.*

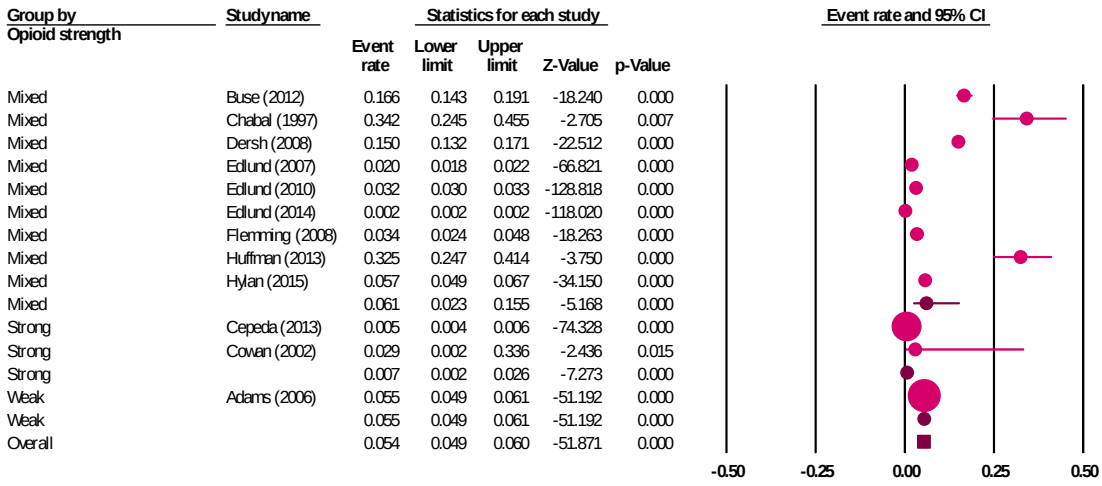


***Figure 5.9**: Sensitivity analysis of the incidence of iatrogenic opioid dependence or abuse by strength of prescription opioid analgesics*

As ***Figure 5.9*** shows, pooled effect estimates of incidence of iatrogenic opioid dependence or abuse differed significantly by whether participants were in receipt of strong opioids, weak opioids or a mix of strong and weak opioids in study samples ($p<0.001$). [It should be noted that, where reported, samples in receipt of 'mixed' opioids were associated with a greater proportion of weak therapeutic opioid use.] Studies where participants were prescribed strong opioids generated a pooled effect of 0.7%, studies where participants were prescribed weak opioids generated a pooled effect of 5.5% and studies where participants were prescribed a mix of strong and weak opioids generated a pooled effect of 6.1%. Meta-regression generated a non-significant model.

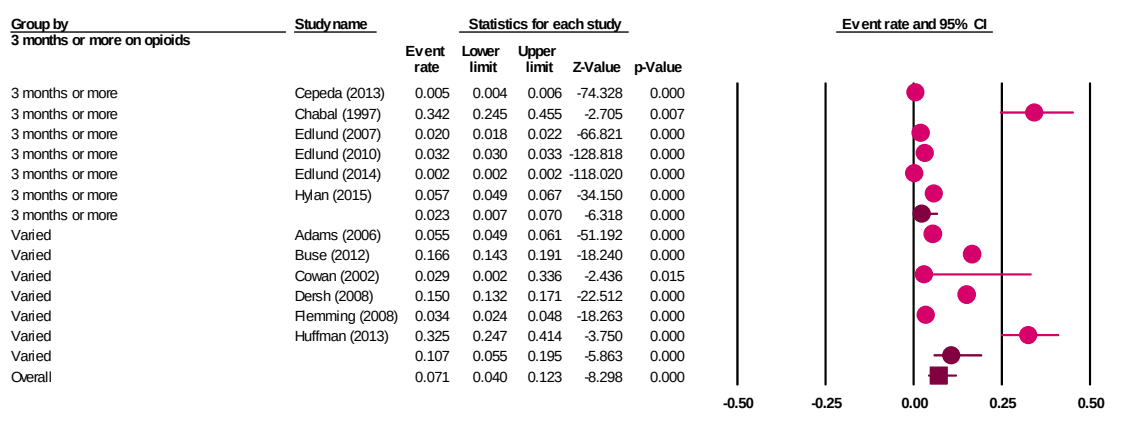


***Figure 5.10:** Sensitivity analysis of the incidence of iatrogenic opioid dependence or abuse by length of exposure to opioid analgesics*

As ***Figure 5.10*** shows, pooled effect estimates of incidence of iatrogenic opioid dependence or abuse differed significantly by duration of exposure to opioid analgesics (p=0.020). Studies where participants were prescribed opioids for 3 months or more generated a pooled effect of 2.3% whilst studies where participants were prescribed opioids for a varied period of time generated a pooled effect of 10.7%. [It should be noted that the participant numbers were relatively small in the sole study where mean length of exposure suggested chronic opioid analgesic therapy (Cowan *et al.* (2012): n=16). Furthermore, In two studies (Flemming *et al.* (2008) and Buse *et al.* (2012)), some participants or all participants, respectively, were in receipt of intermittent, rather than consistent, exposure during an undisclosed period of time. The overall general profile of the 'varied' subgroup suggests relatively short-term, intermittent exposure to therapeutic opioids.] The meta-regression model was statistically significant (Q=3.98; df=1; p<0.005); the regression is shown in ***Figure 5.10***a and the results in ***Table 5.5***.

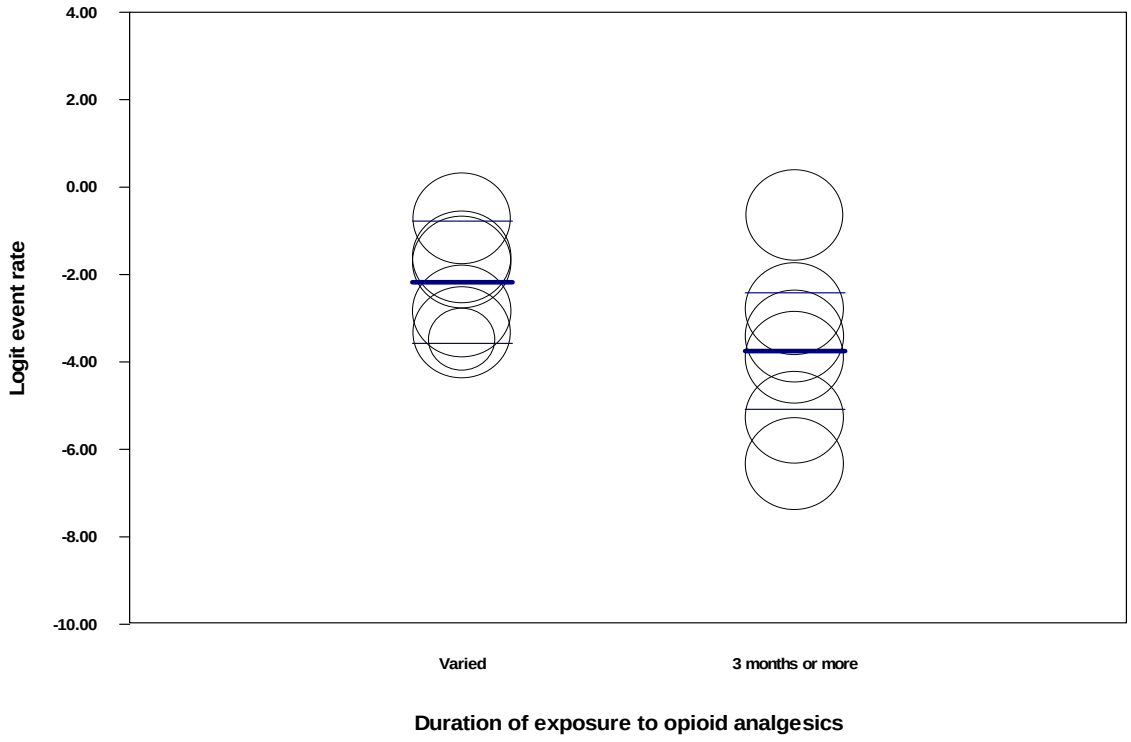
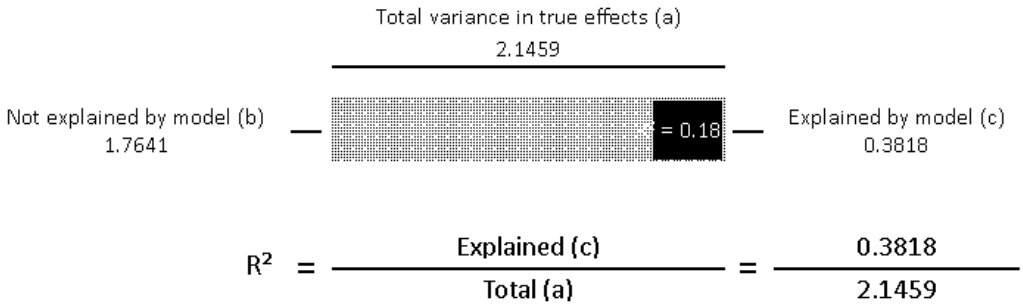


Figure 5.10a: *Regression of logit event rate on opioid analgesic exposure (≥3 months compared with varied duration of exposure) using a random effects (DerSimonian-Laird) model. Regression line and confidence intervals shown in blue.*

Table 5.5: *Random effects (DerSimonian-Laird) meta-regression of duration of logit event rate on opioid analgesic exposure (≥3 months compared with varied duration of exposure) using a Z-distribution*

Covariate	Coefficient	SE	95% lower	95% upper	Z value	p value
Intercept	-2.1772	0.5709	-3.2962	-1.0582	-3.81	0.0001
≥3 months	-1.5727	0.7887	-3.1186	-0.0268	-1.99	0.0462

The coefficient for the moderator variable is negative, indicating that studies where participants were exposed to opioid analgesics for ≥3 months were associated with a mean effect size 1.57 times smaller than studies where participants underwent a mix of acute and chronic exposure. The meta-regression showed that the inclusion of this moderator variable in the regression model explained 18% of the overall variance in study effects (R^2=0.18). ***Figure 5.10b*** shows the R^2 value and an explanation of how this value was ascertained.



(a)	To compute the total variance (about the grand mean) the regression was run with no covariates
(b)	To compute the variance not explained by the model (of all studies about the regression line) the regression was run with the covariate
(c)	The difference between these values gives the variance explained by the model

Figure 5.10b: *R^2 for regression of logit event rate (Z-distribution) on opioid analgesic exposure (≥3 months compared with varied duration of exposure) using a random effects (DerSimonian-Laird) model.*

5.4 Summary of evidence

The primary objective of the current review was to generate a pooled estimate of the incidence of iatrogenic opioid dependence or abuse following exposure to opioid analgesic. Electronic and manual searches, including grey literature searches, were undertaken, and 6164 articles were identified. A total of 2721 duplicates were removed resulting in 3443 articles available for eligibility review. Examination of titles and abstracts determined that 3347 articles were ineligible and, in consequence, 96 articles remained eligible for full text review. A total of 84 articles were excluded during full text review resulting in a total of 12 studies retained for inclusion in the meta-analysis. These 12 studies involved 310,408 participants.

Pooled incidence estimates were generated using the random effects (DerSimonian-Laird method) model. Individual studies were weighted in accordance with the principle of inverse variance and, since a random effects model was applied, this included between-study variance in addition to within-study variance. The overall summary effect indicated an incidence rate of 4.7%, but substantial heterogeneity in study effect sizes was found (99.78%) with incidence rates ranging from 0.2% to 34.2%. Investigation of potential publication bias showed a relatively

symmetrical distribution around the mean, corroborated by non-significant results from the Egger regression intercept (t=0.64; df=10; p=0.536) and the Begg-Mazumdar rank correlation test (Tau=0.15; p=0.493).

In an effort to explain the substantial heterogeneity, a number sensitivity analyses were undertaken. Group differences in summary effects were computed and each variable was entered as a moderator or subgroup variable in a meta-regression. Meta-regression models were run with each of three moderator variables. First, study design was identified using an instrument designed and validated by the Agency for Healthcare Research and Quality (AHRQ). Three study designs were identified in included studies – prospective cohort studies (k=2) were associated with a summary effect of 1.7%, cross-sectional surveys (k=7) were associated with a summary effect of 4.7% and pre-post studies (k=3) were associated with a summary effect of 10.7%. Group differences were non-significant (p=0.432) and meta-regression generated a non-significant model. Second, risk of within study bias was established using instruments designed and validated by the National Institutes of Health (NIH). These instruments generated three possible outcomes: good quality studies; fair quality studies and poor quality studies. Studies identified as fair quality (k=3) generated a summary effect of 15.1% and studies identified as good quality (k=9) generated a summary effect of 3.1%. None of the studies were identified as being 'poor' quality. Group differences were significant (p=0.024) but meta-regression generated a non-significant model. Third, studies were classified according to whether incidence of iatrogenic dependence or abuse was a primary or a secondary objective of the research. Where it was identified as a primary objective of studies (k=8), the summary effect was shown to be 3.0% and, where it was identified as a secondary objective (k=4), the summary effect was shown to be 10.5%. Group differences were non-significant (p=0.058) and meta-regression generated a non-significant model.

Meta-regression models were run with each of three subgroup variables. First, four methods were used in studies to establish a clinical diagnosis of opioid dependence or abuse following opioid analgesic treatment. The use of DSM-IV criteria (k=5) generated a summary effect of 11.3%; use of ICD-9 criteria (k=5) generated a summary effect of 1.3%; use of both criteria together (k=1) generated a summary effect of 2.9%; and clinician assessment (k=1) generated a summary effect of 34.2%. Group differences were significant (p<0.001). The two single-study groups were excluded and the analysis was computed comparing only DSM-IV and ICD-9 criteria. The group difference remained statistically significant (p=0.002). Meta-regression of logit event rate on diagnostic criteria (DSM-IV compared with ICD-9) was undertaken. A statistically significant model was generated (Q=7.77; df=1; p=0.005) and the regression coefficient

indicated that studies using DSM-IV criteria were associated with more than twice the effect than that generated in studies using ICD-9 diagnostic criteria. The model was shown to account for 20% of the variance in study effects.

Second, studies utilising strong opioids, weak opioids or a mix of strong and weak opioids were identified and estimates of pooled subgroup effects were computed. Studies utilising strong opioids only (k=2) generated a summary effect of 0.7%, one study utilised weak opioids only and generated a study effect of 5.5% and studies utilising a mix or strong and weak opioids (k=9) generated a summary effect of 6.1%. Overall group differences were significant ($p<0.001$) and all *post hoc* 2-group comparisons revealed significant differences (all at $p<0.001$).

Third, chronic opioid analgesic exposure was compared with varied exposure (populations where participants underwent a mix of acute and chronic exposure). Studies where participants were prescribed opioids for 3 months (k=6) or more generated a pooled effect of 2.3% whilst studies where participants were prescribed opioids for a varied period of time (k=6) generated a pooled effect of 10.7%. Group differences were statistically significant ($p<0.020$). Meta-regression of logit event rate on duration of opioid analgesic exposure was undertaken. A statistically significant model was generated ($Q=3.98$; $df=1$; $p<0.005$) and the regression coefficient indicated that participants exposed to opioid analgesics for ≥3 months were associated with a mean effect size 1.57 times smaller than studies where participants underwent a mix of acute and chronic exposure. The model was shown to account for 18% of the variance in study effects.

In summary, the incidence of iatrogenic opioid dependence or abuse following opioid analgesic exposure was shown to be 4.7%. Patient groups prescribed strong opioids and exposed to longer-term prescribing were significantly associated with a lower incidence.

5.5 Limitations

The principal limitation of the current review was that, due to pragmatic considerations, included articles were restricted to those written in English. One further limitation is that only 25% of included articles were assessed by a second reviewer. Whilst this is conventional practice, reviews could be strengthened further by all included articles being assessed by a second reviewer.

Chapter 6

Evidence of opioid-induced hyperalgesia in clinical populations: A systematic review and meta-analysis

6.1 Introduction

6.1.1 Rationale

Opioid exposure is associated with a number of debilitating side effects, including the potential for the development of tolerance (Volkow *et al.*, 2016), and dependence and abuse (Fishbain *et al.*, 2008). The development of opioid-induced hyperalgesia (OIH) may represent a substantial additional challenge in the effective treatment of pain. OIH, a paradoxical increase in pain sensitivity following opioid exposure, is thought to result from sensitisation of pain signalling pathways, and there is evidence to suggest a dose-dependent relationship with opioids (e.g. Ackerman, 2006; Axelrod *et al.*, 2007; Chung *et al.*, 2004; Mercadante *et al.*, 2005; Hooten *et al.*, 2010). In consequence, OIH may be treated effectively by opioid rotation, reduction or cessation, as recommended in SIGN 136 (SIGN, 2013). OIH has been well-documented in preclinical studies; however, the translatability of these findings to clinical settings is questionable (Vierck *et al.*, 2008). The literature concerning clinical populations is sparse and less consistent in its findings (Angst *et al.*, 2016; Eisenberg *et al.*, 2015); however, clinical experience suggests that OIH is a relatively common but under-recognised phenomenon (Zylicz *et al.*, 2008).

OIH is generally thought to arise following neuroplastic changes in the central and peripheral nervous systems that result in sensitisation of pronociceptive pathways; however, the exact molecular mechanisms are not well-understood (Lee *et al.*, 2011; Chu *et al.*, 2011; Younger *et al.*, 2011). Whilst there are several proposed central and peripheral mechanisms, such as alpha-2 adrenoceptors and the endocannabinoid system, the most prominent of these is considered to be the potential role of the central glutaminergic system, suggesting that opioid exposure increases N-methyl-D-aspartate (NMDA) activity. It is, therefore, proposed that NMDA receptor antagonists may attenuate OIH and, indeed, this has been demonstrated in several studies (e.g. King *et al.*, 2005; Ossipov *et al.*, 2005; Mao, 2006)

The development of effective policy and practice relies on direction from robust evidence bases. Given the predominance of case reports in this field of study, an initial step towards understanding the clinical relevance of this phenomenon may involve synthesis of currently-available empirical data from larger-scale studies. This should not only include verification of the phenomenon in clinical settings, but also examination of how treatment characteristics impact on the potentiation and attenuation of hyperalgesic states. This may include factors such as: treatment setting (opioid replacement therapy or analgesic treatment); duration of opioid exposure; therapeutic opioid dose; and the role of adjunctive treatments such as NMDA receptors antagonists.

6.1.2 Objectives

The core objective of the current review was to undertake a systematic review and meta-analysis of studies examining evidence for OIH in humans following chronic opioid exposure. OIH was assessed by examining pain threshold and tolerance in response to noxious thermal (hot and cold), electrical and mechanical stimuli. Included studies were restricted to those that undertook quantitative sensory testing (QST) of non-painful sites since examination of painful sites or patient-reported pain scales may be more likely to reflect presence of tolerance rather than, specifically, opioid induced hyperalgesia. The primary hypothesis was, therefore:

- OIH will be evident in patients following chronic opioid exposure, evidenced by decreased pain threshold and/or pain tolerance, compared with controls, using QST metrics.

The secondary objectives were to examine subgroups and to attempt to explain any heterogeneity found in study effects. Three subgroup variables and one moderator variable were used to examine four hypotheses:

- Evidence of OIH will differ by treatment group (treatment for opioid dependence versus treatment for chronic pain);
- Decreased evidence of OIH will be associated with opioids with NMDA receptor antagonist properties;
- Increased evidence of OIH will be associated with increasing opioid treatment dose;
- Evidence of OIH will differ by study quality (whether studies were identified as ‘good’ or ‘fair’ quality).

6.2 Methods

The established PICOS framework (**P**opulation, **I**nterventions, **C**omparators, **O**utcomes and **S**tudy design) was used to design the current review and to develop an appropriate search

strategy. The findings are reported in accordance with the recommendations set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher, 2009).

6.2.1 Protocol and registration

The review protocol was registered on PROSPERO, the international database of prospectively registered systematic reviews in health and other related domains of study. A copy of the PROSPERO registration can be found in Appendix IV. The protocol registration number is CRD42017058513 and it can be accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017058513.

6.2.2 Eligibility criteria

Searches were undertaken on 1 April 2017 and no date restrictions were applied; eligible articles were restricted to those written in the English language.

Populations were included if they were human and in receipt of chronic opioid therapy for the treatment of either opioid dependence or pain. Animal models and *in vitro* models were excluded.

Interventions took the form of opioid analgesic treatment or opioid replacement therapy (ORT) for the treatment of opioid dependence. Data were extracted from all studies where participants were exposed to opioids for 1 month or more. Studies were excluded if they focused on acute opioid exposure (<1 month) – this primarily included the delivery of opioids during the perioperative period and exposure in healthy volunteers.

Comparator populations were included from several clinical settings and study designs. Healthy volunteers were included as were patients in receipt of non-opioid analgesics when compared with opioid exposure in patients with chronic pain. Single-sample repeated measures designs were also included if patients initiated or ceased use of opioids.

Outcomes were extracted for all available experimental pain modalities and were confined to findings from quantitative sensory testing (QST) techniques. Studies were excluded if they relied upon patient-reported visual analogue scales (VAS) or numerical rating scales (NRS) of pain intensity, or if pain assessment was based on cumulative opioid dose required to manage pain symptoms.

Study designs that were excluded were secondary data (to avoid duplication of articles presenting primary data) and case reports (due to the absence of control data). Furthermore, a sample size of one would result in poor study precision within a meta-analysis and case reports are generally written to highlight exceptional findings (they may not be considered to be generalisable and would be likely to introduce publication bias, since non-significant case reports are rarely published).

6.2.3 Information sources

Electronic searches were undertaken using: Embase; Medline; PubMed; Cinahl Plus; Web of Science and OpenGrey. Searches were run on 1 April 2017 and no date restrictions were applied. A manual search of the references of included publications was also undertaken. In an attempt to avoid publication bias, a broad manual grey literature search was undertaken; this included examination of conference proceedings, technical reports, organisation websites and dissertations. At a later stage, once included articles had been identified, a manual reference search was undertaken of these included articles.

6.2.4 Search

The search term was constructed using the PICOS principles, shown below, and was run in each of the electronic databases. The English language filter was applied in all databases and the participants filter (human only) was applied where available (Embase, Medline and PubMed).

- ***Population:*** opi*
- ***Intervention:*** Not included in search strategy
- ***Comparators:*** Not included in search strategy
- ***Outcomes:*** hyperalg* OR OIH OR "pain sensit*" OR "pain toler*" OR PTO OR "pain thresh*" OR PTR
- ***Study design:*** Not included in search strategy

6.2.5 Study selection

Initially, articles underwent title and abstract review. Where articles clearly did not meet inclusion criteria, they were excluded, and the reason for exclusion was recorded. Remaining articles underwent full text eligibility review, in light of careful consideration of the inclusion and exclusion criteria, and the reason for each article excluded at this stage was recorded. A random selection of 25% of included articles was assessed by a second reviewer who was blind to title, author, journal and year of publication.

6.2.6 Data collection process

A data extraction proforma was designed and piloted with 5 of the included articles. Whilst it was evident that there would not be a full complement of data available for subgroup analyses, all items were retained in the proforma for assessment following the extraction of available data from all included articles. Where required, authors were contacted in an effort to seek clarification of the data presented in articles. A number of issues were encountered and, in the interests of transparency, they are discussed in this section. First, several studies reported

findings visually and, therefore, the data extracted from these articles were obtained from graphs rather than more precise numerical reports. Secondly, where studies reported data at individual patient level, means and standard deviations were calculated. Thirdly, where data were reported at subgroup level only (e.g. 'morphine group' and 'methadone group'), the overall means and standard deviation were calculated.

6.2.7 Data items

Data items were extracted and recorded on a pre-piloted proforma. The data items that were extracted for each study (where available) were: author(s); article title; date of publication; study design; number recruited and final number included in sample; treatment group (opioid-dependent or chronic pain); demographic characteristics (gender composition, mean age and ethnic composition); psychiatric characteristics (depression and anxiety scores); duration of pain (where applicable); prescription drug information (name of drug, length of exposure to drug and mean morphine-equivalent daily dose); core outcomes (pain threshold and tolerance values); pain modality; evidence of attempts to control for tolerance; evidence of use of opioids with NMDA receptor antagonist properties; and additional notes (free text box in which explanatory notes or issues for consideration were recorded).

6.2.8 Risk of bias in individual studies

Assessment of risk of bias in individual studies was undertaken at study level, rather than outcome level, and was achieved using instruments designed by the National Institutes of Health (NIH). A copy of the two instruments used in the present review can be found in Appendices I and II, and copies can be located online at:

- Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group (**URL: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after**)
- Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies **(URL: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort**)

These instruments are not intended to be summed to provide a total score, since assigning scores may be considered to be misleading (Greenland, 2001). Instead, these instruments are designed to prompt consideration of the key concepts relating to internal validity and potential risk of bias in individual study designs. As such, study quality was rated as: 'poor'; 'fair'; or 'good'. These results were entered into the review dataset as a moderator variable and used in meta-regressions.

6.2.9 Summary measures

The principal measure used in the primary meta-analysis and in subgroup analyses was standardised mean difference (SMD) between cases and controls. To facilitate this computation, data were extracted for mean group threshold and tolerance values, standard deviations around the mean and number of participants in group (for both the case and control groups). Pain threshold (PTR) refers to stimulus intensity/time taken to detect pain. Pain tolerance (PTO) refers to stimulus intensity/time taken to withdraw from the stimulus.

6.2.10 Synthesis of results

Pooled study effect estimates were generated using the random effects (DerSimonian-Laird method) model. Individual studies were weighted in accordance with the principle of inverse variance and, since a random effects model was applied, this included between-study variance in addition to within-study variance. The weighted contribution of each study is reflected in its respective symbol size in each forest plot. The decision to use a random effects model was made *a priori* since it was clear that studies would differ on population characteristics such as age distribution, gender distribution, ethnicity, cultural background, socioeconomic status and a range of clinical characteristics. Using the random effects model, the Cochran's *Q* statistic and the I^2 statistic assessed both within-study and between-study heterogeneity. Whilst the pooled estimated effect size shown in fixed and random effects models can be similar, since the random effects model incorporates an estimate of between-study variance it is, therefore, likely to generate wider confidence intervals.

Heterogeneity is a measure of inconsistency in study outcomes across all studies in a meta-analysis. The classical measure of heterogeneity is Cochran's Q statistic; it is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies (with weights being those used in the pooling method) and is distributed as a chi-square statistic (number of studies minus one degree of freedom). In consequence, the power of Cochran's Q varies according to the number of included studies. The I^2 statistic is not, however, dependent upon the number of included studies (100% x (Q-df)/Q).). All relevant computations were presented (Cochran's Q; Tau^2; and I^2) but the preferred I^2 statistic (Higgins & Thompson, 2002) was used to classify heterogeneity. Definitive heterogeneity thresholds can be misleading; however, The Cochrane Handbook (section 9.5.2) provides a guide to interpreting the I^2 statistic and suggests that ≥50% may represent substantial heterogeneity.

6.2.11 Risk of bias across studies

Publication bias may lead to nonsignificant or 'negative' findings being more likely to remain unpublished and therefore this represents an essential component of systematic reviews and meta-analyses. Publication bias was assessed using the Egger regression intercept bias detection test rather than the Begg-Mazumdar rank correlation test since, comparatively, it is more sensitive to a range of bias types and does not lose power to the same degree when assessing a smaller number of studies. The use of imputational strategies in meta-analyses remains controversial and, furthermore, are unlikely to alter the conclusions in over 90% of secondary data analyses (Sutton *et al.*, 2000). In consequence, imputational strategies were not used in the current review.

6.2.12 Additional analyses

Subgroup/moderator analyses were undertaken in an effort to examine secondary hypotheses, and meta-regression (DerSimonian-Laird method) was performed in an attempt to explain substantial heterogeneity. Subgroup analyses were undertaken based on treatment characteristics: treatment for opioid dependence or chronic pain; whether or not the opioid had NMDA receptor antagonist properties; and opioid dose used in treatment. Moderator analyses were undertaken for quality assessment of individual articles. Further subgroup analyses were planned for a range of demographic and clinical characteristics (including duration of opioid exposure) but, due to insufficient data, these analyses were not undertaken. Within the scope of the current review there were insufficient studies to undertake meta-regression with more than one subgroup variable in each analysis.

6.3 Results

6.3.1 Study selection

Electronic searches identified 6121 articles and a further 46 were identified through manual searches. A total of 1831 duplicates were identified resulting in a total of 4336 articles retained for eligibility review. ***Figure 6.1*** shows the total number of articles that underwent eligibility review and the total number of articles included in the current review underwent full-text review.

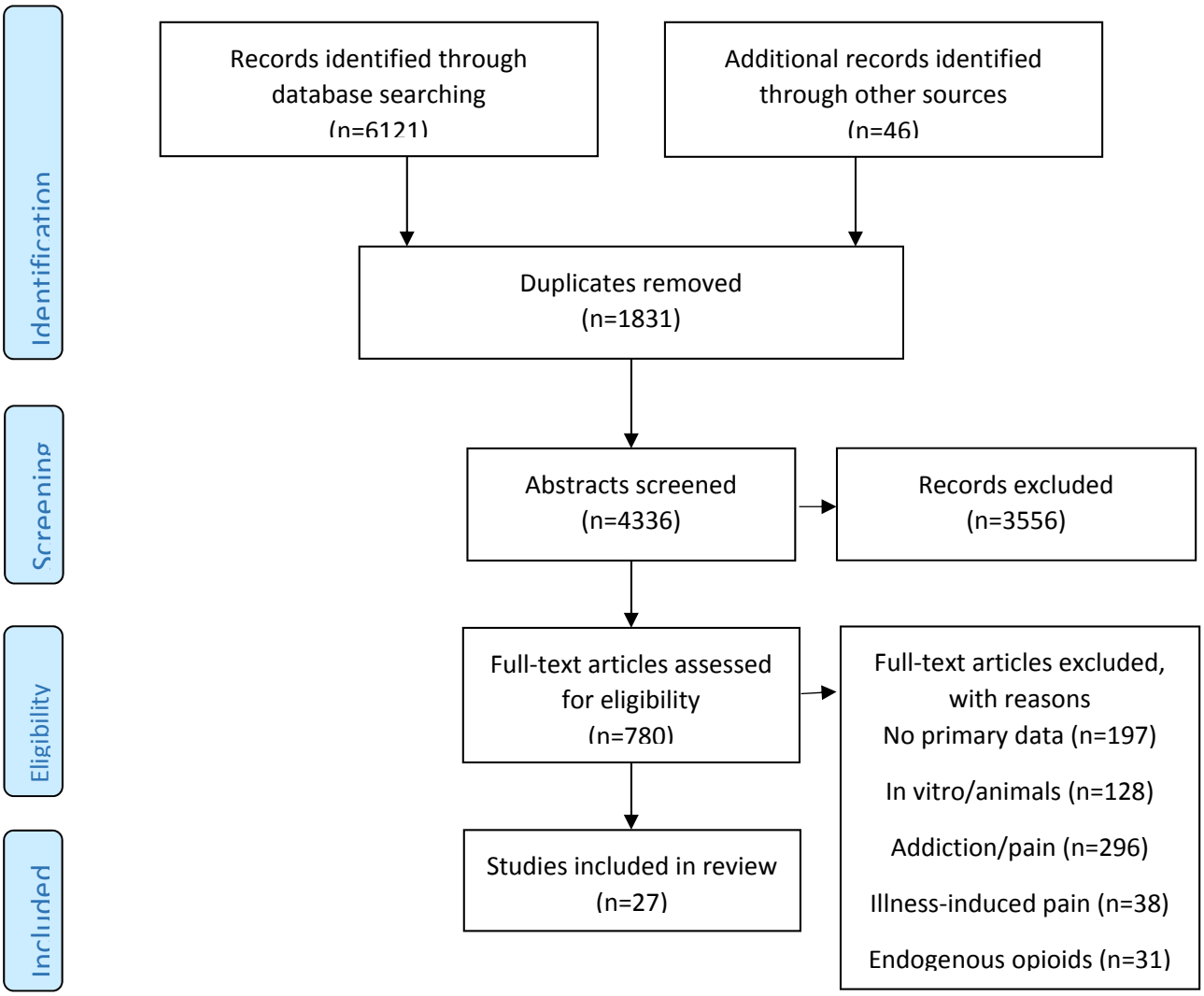


Figure 6.1: *Total number of articles excluded on eligibility review and number of articles retained for inclusion in current review.*

Where the same author contributed to more than one included study, articles were reviewed to ensure that participants were not double-counted within the current review. Data were extracted from 27 articles, involving a total of 2780 participants. The number of articles included for each research question is shown in ***Figure 6.2***.

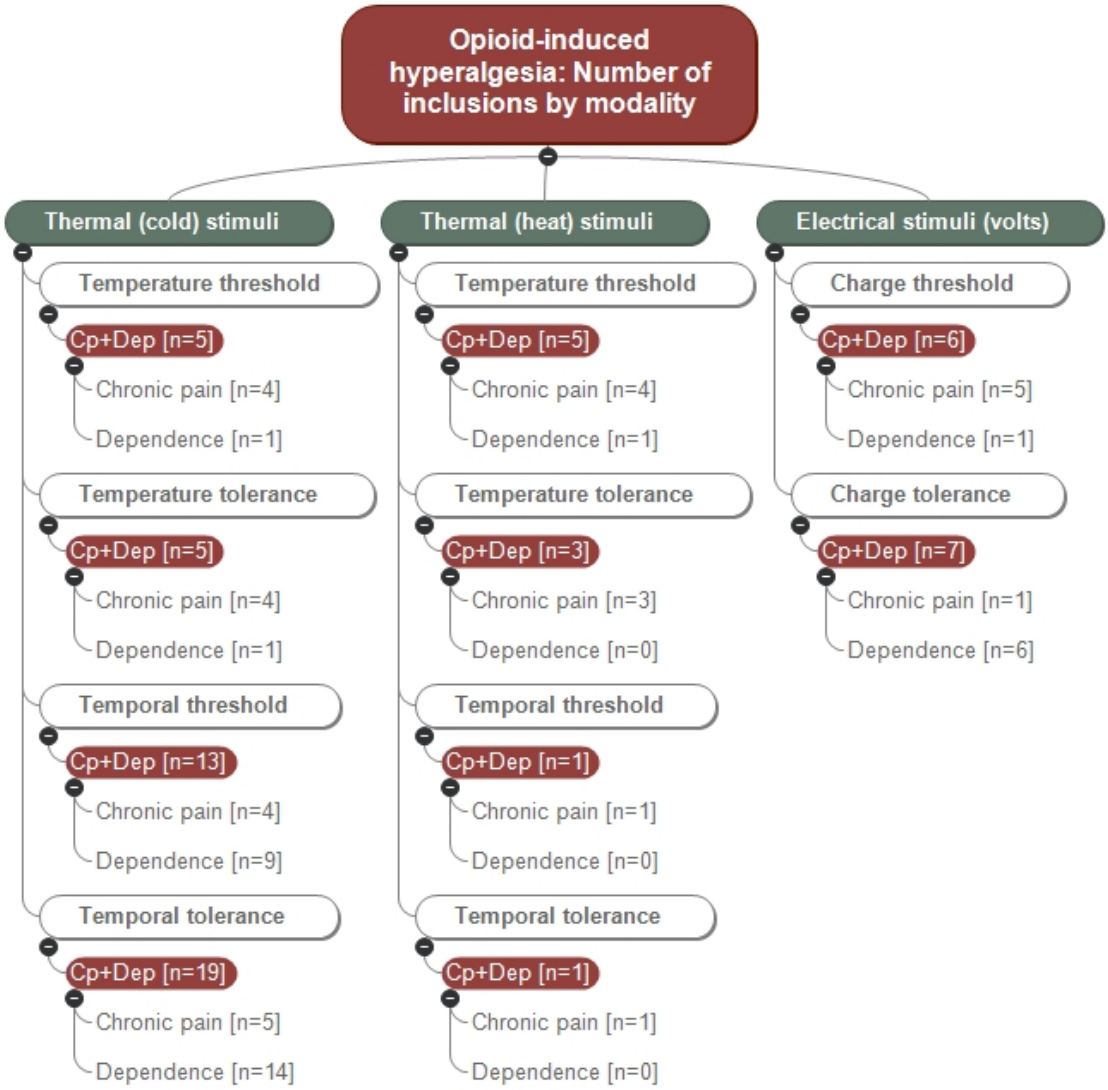


Figure 6.2: *Number of samples (n=76) included in the review, by research section. Where meta-analyses or qualitative syntheses were planned, these numbers are shaded in dark red. Beneath that are the numbers included in each treatment group. Meta-analyses were undertaken where data were available from three or more studies. [Cp=chronic pain; Dep=opioid dependence.]*

Regarding mechanical stimuli, articles provided different metrics (e.g. kPa, Newtons, oz, etc.). An attempt was made to convert means and standard deviations to one consistent metric (kPa); however, the converted data were not deemed to be reliable and, in consequence, data for mechanical stimuli were not pooled. Converted values differed, implausibly, by two orders of magnitude. This may have resulted from insufficient data reported in original articles – i.e. a measure of force, but not area, was reported in these articles; for example, 'Newtons' rather than 'Newtons per m^{2}' or 'Newtons per cm^{2}'. Whilst the appropriate SI unit was used in each computation (Newtons per m^2 in this particular example) this may not have accurately reflected the force applied in studies. Data from the remaining three modalities were pooled. Following

the removal of articles reporting solely mechanical pain (k=1), 26 articles were retained involving 2706 participants. The shaded numbers in ***Figure 6.2*** indicate the number of included articles relating to each research question within the three pain modalities. Since bias assessment functions do not work well with less than three studies, meta-analyses were not undertaken where there were less than three studies per research question. In consequence, data for cold (temperature) tolerance, heat (temporal) threshold and heat (temporal) tolerance were synthesised qualitatively.

6.3.2 Study characteristics

The characteristics of included studies are shown in ***Table 6.1***. Where the outcome measures for the current review were not a primary objective or were not the only primary objective, the study design was reported for the method used to obtain the relevant data rather than the method used in the overall study. Study design was identified using Agency for Healthcare Research and Quality (US DoH) criteria (AHRQ, 2011).

Table 6.1: *Characteristics of included studies (n=26)*

Author (year)	N	Study design	Study effect			
			Pain threshold		Pain tolerance	
			Cases	Controls	Cases	Controls
Athanasos (2006) – opioid dependence treatment group						
Cold (seconds)	28	Cross-sectional	----	----	15	34
Electrical (volts)	28	Cross-sectional	----	----	54	65
Chen (2009) – chronic pain treatment group						
Cold (Celsius)	99	Cross-sectional	10.9	8.4	3.3	0.5
Heat (Celsius)	99	Cross-sectional	43.8	45.3	48.6	50.1
Chu (2006) – chronic pain treatment group						
Cold (seconds)	6	Pre-post	12.1	10.1	28.0	19.8
Compton (1994) – opioid dependence treatment group						
Cold (seconds)	220	Cross-sectional	----	----	62	86.1
Compton (2000) – opioid dependence treatment group						
Cold (seconds)	120	Cross-sectional			43.7	93.9
Compton (2001) – opioid dependence treatment group						
Cold (seconds)	54	Cross-sectional			60.4	138
Compton (2012) – opioid dependence treatment group						
Cold	103	Cross-sectional	9.38	11.79	18.26	41.54
Electrical (volts)	103	Cross-sectional	41.54	38.00	56.07	63.55
Doverty (2001) – opioid dependence treatment group						
Cold (seconds)	8	Cross-sectional	7.3	7.4	25	57
Electrical (volts)	8	Cross-sectional	37	28	63	52
Doverty (2001a) – opioid dependence treatment group						
Cold (seconds)	32	Cross-sectional	4	5	21	63
Electrical (volts)	32	Cross-sectional	34	28	54	63
Edwards (2011) – chronic pain treatment group						
Cold (seconds)	276	Cross-sectional	15	18.32	----	45
Heat (seconds)	276	Cross-sectional	42	41	----	45

Edwards (2016) – chronic pain treatment group						
Cold (seconds)	31	Pre-post	----	----	40	40
Eisenberg (2007) – opioid dependence treatment group						
Cold (seconds)	113	Cross-sectional	10.5	7.1	30.5	55.2
Hay (2009) – chronic pain treatment group						
Electrical (volts)	30	Cross-sectional	35.6	34.8	48.1	52.6
Cold (seconds)	30	Cross-sectional	10.75	12.2	18.9	30.7
Hay (2009) – opioid dependence treatment group						
Electrical (volts)	20	Cross-sectional	38.8	34.8	52.4	52.6
Cold (seconds)	20	Cross-sectional	8.9	12.2	18.9	30.7
Hina (2015) – chronic pain treatment group						
Heat (Celsius)	68	Cross-sectional	43	43.5	47.1	48.4
Ho (2011) – opioid dependence treatment group						
Cold (seconds)	111	Cross-sectional	11	9	24	34
Krishnan (2012) – opioid dependence treatment group						
Electrical (volts)	32	Cross-sectional	63.5	37	65.5	59
Peles (2010) – opioid dependence treatment group						
Cold (Celsius)	48	Cross-sectional	19.5	17.5	----	----
Heat (Celsius)	48	Cross-sectional	44	43	----	----
Pud (2006) – opioid dependence treatment group						
Cold (seconds)	130	Cross-sectional	10.6	6.6	29.1	56.4
Ram (2009) – chronic pain treatment group						
Cold (seconds)	110	Cross-sectional	9.9	10.1	22.8	24.1
Reznikov (2005) – chronic pain treatment group						
Heat (Celsius)	224	Cross-sectional	45.4	45.7	----	----
Suzan (2013) – chronic pain treatment group						
Cold (seconds)	40	Cross-sectional	----	----	43.9	30.0
Treister (2012) – opioid dependence treatment group						
Cold (seconds)	100	Cross-sectional	10.8	6.8	30.0	56.4
Wachholtz (2014) – chronic pain treatment group						
Cold (seconds)	90	Cross-sectional	24.22	54.4	53.3	137.1
Wang (2012) – chronic pain treatment group						
Cold (Celsius)	63	Cross-sectional	11	9	----	----
Heat (Celsius)	63	Cross-sectional	42	47	----	----
Zahari (2016) – opioid dependence treatment group						
Cold (seconds)	300	Cross-sectional	----	----	34.17	61.36
Zhang (2015) – chronic pain treatment group						
Heat (Celsius)	250	Cross-sectional	43.7	44.7	48.8	49.9
Cold (Celsius)	250	Cross-sectional	11.2	9.4	3.88	0.56

6.3.3 Risk of bias within studies

Risk of bias within studies was undertaken at study level, rather than at outcome level, and assessed using instruments designed by the National Institutes of Health (NIH). These instruments generated categorical data pertaining to the design of individual studies (poor; fair; and good quality). Results are reported in ***Table 6.2*** along with a justification of any studies not identified as 'good' quality.

Table 6.2: *Risk of bias within studies (k=26)*

Author (year)	Study quality	Justification
Athanasos (2006)	Fair	Small number of participants and no power calculations
Chen (2009)	Good	Not applicable
Chu (2006)	Fair	Small number of participants and no power calculations
Compton (1994)	Good	Not applicable
Compton (2000)	Good	Not applicable
Compton (2001)	Fair	Small number of participants and no power calculations
Compton (2012)	Good	Not applicable
Doverty (2001)	Fair	Small number of participants and no power calculations
Doverty (2001a)	Good	Not applicable
Edwards (2011)	Good	Not applicable
Edwards (2016)	Good	Not applicable
Eisenberg (2007)	Good	Not applicable
Hay (2009)	Good	Not applicable
Hina (2015)	Good	Not applicable
Ho (2011)	Good	Not applicable
Krishnan (2012)	Fair	Small number of participants and no power calculations
Peles (2010)	Good	Not applicable
Pud (2006)	Good	Not applicable
Ram (2009)	Good	Not applicable
Reznikov (2005)	Good	Not applicable
Suzan (2013)	Fair	30 cases but only 10 controls – small number, unbalanced groups
Treister (2012)	Good	Not applicable
Wachholtz (2014)	Good	Not applicable
Wang (2012)	Good	Not applicable
Zahari (2016)	Good	Not applicable
Zhang (2015)	Good	Not applicable

6.3.4 Synthesis of results

6.3.4.1 Pain threshold

Figures 6.3 - 6.6 show the study effects and overall summary effects for pain threshold (PTR) in response to thermal (cold and heat) and electrical experimental pain. A forest plot is not included for heat threshold assessed in seconds tolerated; due to the small number of studies (k=1), data from that study were synthesised qualitatively. Individual studies were weighted in accordance with the principle of inverse variance and, since a random effects model was applied, this included between-study variance in addition to within-study variance.

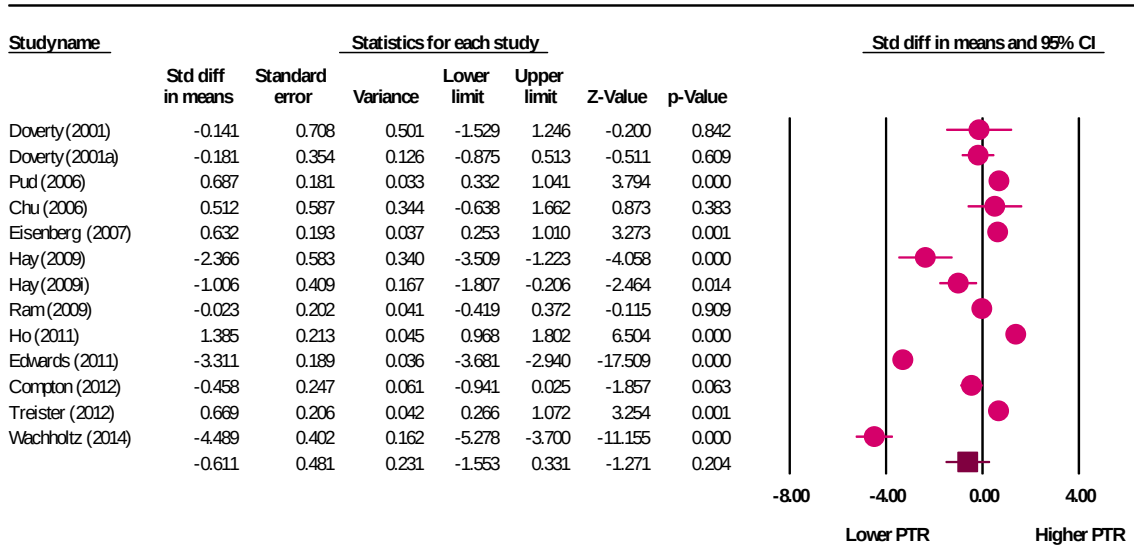


Figure 6.3: *Meta-analysis (random effects model) – pooled study findings of pain threshold (PTR) in response to thermal (cold) experimental pain, measured in seconds to pain detection, at a non-painful site in patients in receipt of chronic opioid therapy.*

The summary effect, the weighted standardised mean difference between cases and controls using a random effects model, is shown to be non-significant. The included studies are listed in ***Figure 6.3*** in chronological order of date of publication and it is shown that there is no pattern associated with findings over time.

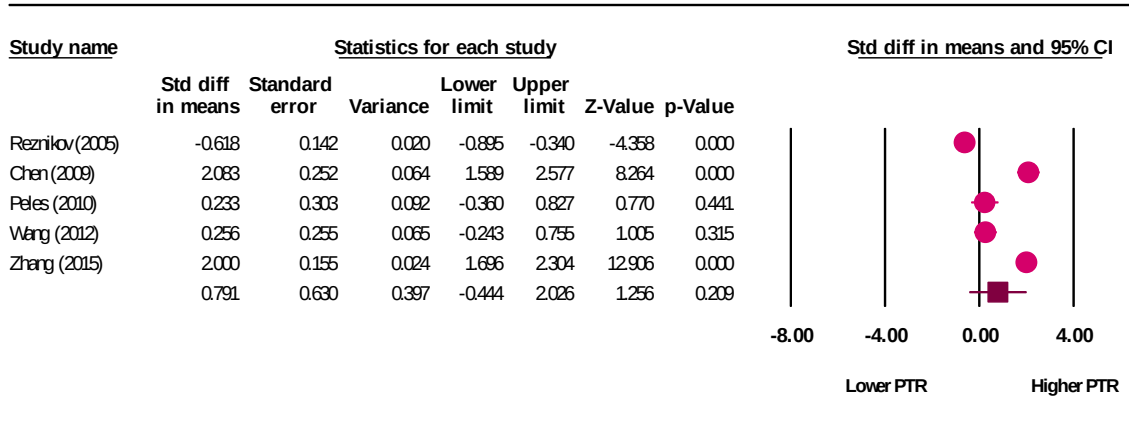


Figure 6.4: *Meta-analysis (random effects model) – pooled study findings of pain threshold (PTR) in response to thermal (cold) experimental pain, measured in degrees Celsius to pain detection, at a non-painful site in patients in receipt of chronic opioid therapy.*

The summary effect, the weighted standardised mean difference between cases and controls using a random effects model, is shown to be non-significant. The included studies are listed in

Figure 6.4 in chronological order of date of publication and it is shown that there is no pattern associated with findings over time.

One study reported heat pain threshold measured in seconds to pain detection (Edwards, 2011). Findings were very similar for cases and controls whereby pain detection occurred at 42 seconds and 41 seconds, respectively, in response to a noxious thermal (heat) stimulus.

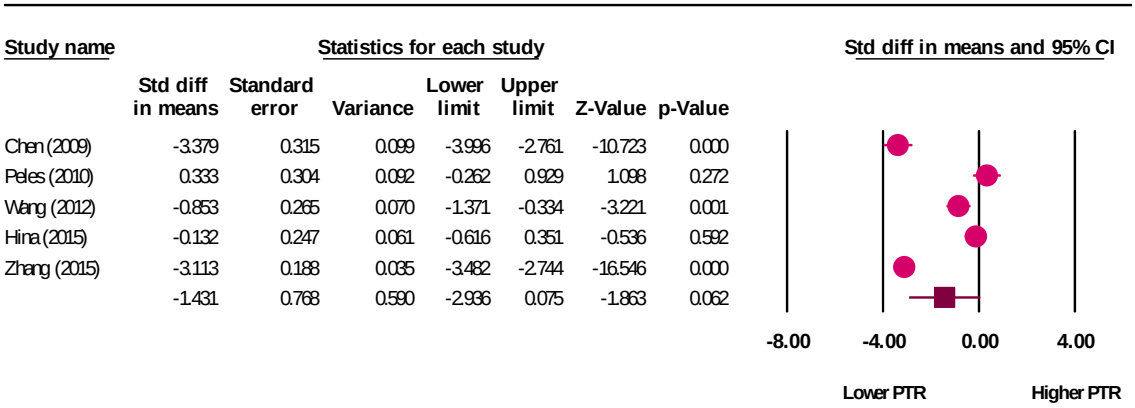


Figure 6.5: *Meta-analysis (random effects model) – pooled study findings of pain threshold (PTR) in response to thermal (heat) experimental pain, measured in degrees Celsius to pain detection, at a non-painful site in patients in receipt of chronic opioid therapy.*

The summary effect, the weighted standardised mean difference between cases and controls using a random effects model, was shown to be non-significant. The included studies are listed in ***Figure 6.5*** in chronological order of date of publication and it is shown that there is no pattern associated with findings over time.

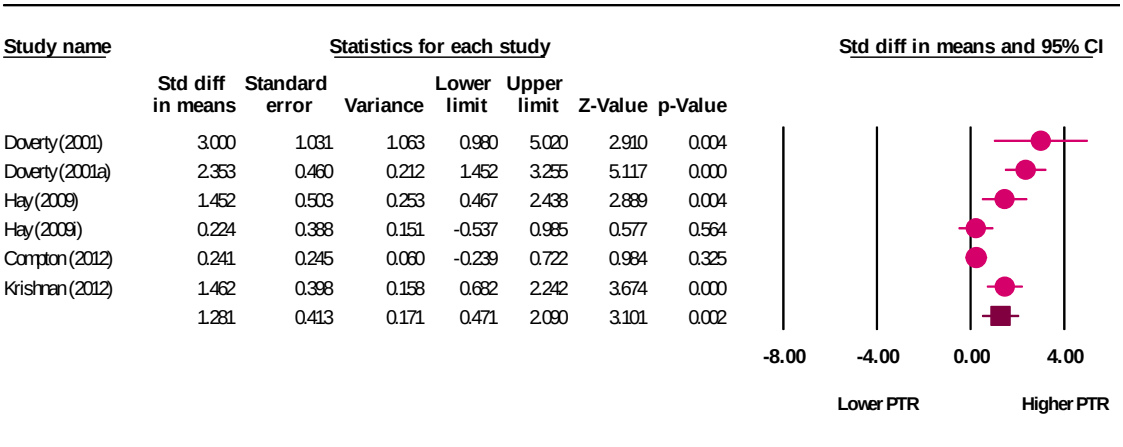


Figure 6.6: *Meta-analysis (random effects model) – pooled study findings of pain threshold (PTR) in response to electrical experimental pain, measured in volts to pain detection, at a non-painful site in patients in receipt of chronic opioid therapy.*

The summary effect, the weighted standardised mean difference between cases and controls using a random effects model, was shown to be +1.281 (95% CI = 0.5 to 2.1), indicating significantly higher pain threshold (and, consequently, lower pain sensitivity) in patients in receipt of opioid therapy, compared with controls, in response to a noxious electrical stimulus ($p<0.001$). The included studies are listed in ***Figure 6.6*** in chronological order of date of publication and it is shown that, with the exception of the most recent study, the difference between cases and controls diminished over time. Interestingly, the sole study that deviates from this pattern is reported to be of 'fair' rather than 'good' quality due to the small number of participants included in the study. Substantial heterogeneity was identified in study effects ($I^2=81.87$) [$Q=27.6$ ($df=5$); $p<0.001$; $Tau^2=0.78$ ($SE=0.67$; $Variance=0.45$; $Tau=0.88$)]. Heterogeneity was anticipated, hence the *a priori* decision to employ the use of a random effects model, and this will be examined further in subgroup/moderator analyses.

Five of the six study samples that underwent pain threshold assessment in response to noxious electrical stimuli also underwent pain threshold assessment in response to noxious thermal (cold) stimuli measured in seconds tolerated (Doverty, 2001; Doverty 2001a; Hay, 2009 (opioid-dependent sample); Hay, 2009i (chronic pain sample); and Compton, 2012). The sixth sample (Krishnan, 2012) did not undergo thermal QST assessment of pain threshold. The pooled effect estimate of these five studies, in response to noxious thermal (cold) stimuli, is shown in ***Figure 6.6a***.

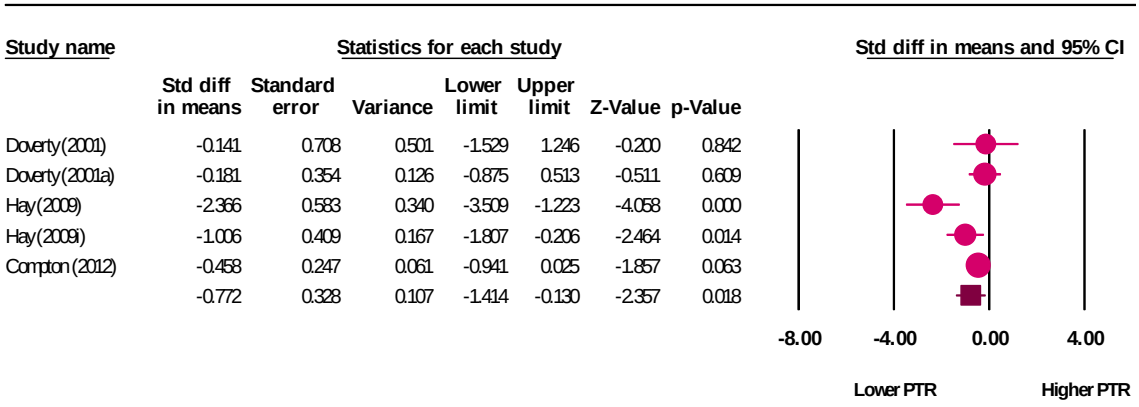


Figure 6.6a: *Meta-analysis (random effects model) – pooled study findings of pain threshold (PTR) in response to thermal (cold) experimental pain, measured in seconds tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

Contrary to the findings of electrical experimental pain, the findings relating to thermal (cold) pain in the same samples lay in the opposite direction – cases were associated with significantly lower pain threshold compared with controls. The weighted standardised mean difference between cases and controls, using a random effects model, is shown to be -0.772 (95% CI = -1.414 to -0.130), indicating significantly lower pain threshold (and, consequently, higher pain sensitivity) in patients in receipt of opioid therapy, compared with controls, in response to a noxious cold stimulus (p=0.018).

6.3.4.2 Pain tolerance

Figures 6.7 - 6.9 show the study effects and overall summary effects for pain tolerance (PTO) in response to thermal (cold and heat) and electrical experimental pain. Forest plots are not included for cold tolerance measured in degrees Celsius (k=2) or for heat tolerance measured in seconds (k=1); data from these studies were synthesised qualitatively. Individual studies were weighted in accordance with the principle of inverse variance and, since a random effects model was applied, this included between-study variance in addition to within-study variance.

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Compton (1994)	-0.294	0.171	0.029	-0.629	0.040	-1.725	0.085
Compton (2000)	-0.590	0.187	0.035	-0.956	-0.225	-3.165	0.002
Compton (2001)	-0.795	0.299	0.089	-1.380	-0.210	-2.662	0.008
Doverty (2001)	-7.541	2.014	4.055	-11.488	-3.595	-3.745	0.000
Doverty (2001a)	-7.379	0.988	0.976	-9.315	-5.443	-7.470	0.000
Chu (2006)	0.775	0.599	0.358	-0.398	1.949	1.295	0.195
Athanasos (2006)	-4.893	0.764	0.583	-6.390	-3.397	-6.408	0.000
Pud (2006)	-0.605	0.180	0.032	-0.957	-0.252	-3.361	0.001
Eisenberg (2007)	-0.549	0.192	0.037	-0.925	-0.173	-2.862	0.004
Hay (2009)	-3.942	0.639	0.409	-5.195	-2.688	-6.164	0.000
Ram (2009)	-0.051	0.202	0.041	-0.446	0.345	-0.252	0.801
Hay (2009i)	-3.847	0.755	0.570	-5.326	-2.367	-5.095	0.000
Ho (2011)	-1.548	0.218	0.048	-1.975	-1.121	-7.103	0.000
Compton (2012)	-1.417	0.264	0.070	-1.933	-0.900	-5.371	0.000
Treister (2012)	-0.594	0.204	0.042	-0.994	-0.193	-2.906	0.004
Suzan (2013)	0.318	0.367	0.135	-0.401	1.037	0.867	0.386
Wachholtz (2014)	-6.458	0.531	0.282	-7.499	-5.418	-12.168	0.000
Edwards (2016)	0.000	0.254	0.065	-0.498	0.498	0.000	1.000
Zahari (2016)	-2.949	0.167	0.028	-3.276	-2.622	-17.678	0.000
	-1.833	0.319	0.102	-2.458	-1.208	-5.750	0.000

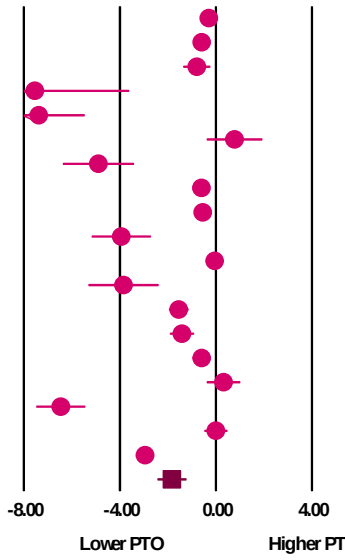


Figure 6.7: *Meta-analysis (random effects model) – pooled study findings of pain tolerance (PTO) in response to thermal (cold) experimental pain, measured in seconds tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

The summary effect, the weighted standardised mean difference between cases and controls using a random effects model, is shown to be -1.833 (95% CI = -2.5 to -1.2), indicating

significantly lower pain tolerance (and higher pain sensitivity) in patients in receipt of opioid therapy, compared with controls, in response to a cold noxious stimulus (p<0.001). The included studies are listed in **Figure 6.7** in chronological order of date of publication and it is shown that there is no pattern associated with findings over time. Substantial heterogeneity was identified in study effects (I^2=96.09) [Q=461 (df=18); p<0.001; Tau^2=1.68 (SE=0.74; Variance=0.55; Tau=1.30)]. Heterogeneity was anticipated, hence the *a priori* decision to employ the use of a random effects model, and this will be examined further in subgroup/moderator analyses.

Two studies reported cold pain tolerance assessed by degrees Celsius tolerated (Chen, 2009; Zhang, 2015). In both studies cases were associated with lower tolerance (and, consequently, higher sensitivity). Cases tolerated temperatures of 3.30 and 3.88 degrees Celsius, respectively, as compared with 0.50 and 0.56 degrees Celsius, respectively, in the control groups.

One study reported heat pain tolerance assessed by seconds tolerated (Edwards, 2011). Findings were identical for cases and controls whereby the noxious heat stimulus was tolerated for 45 seconds in both groups.

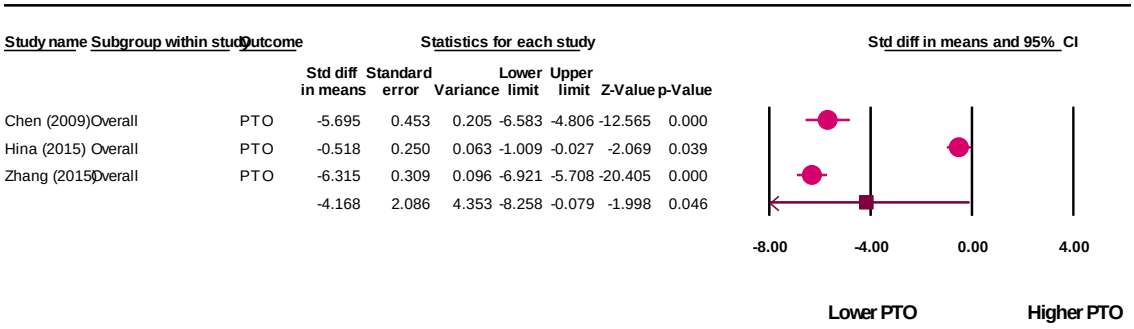


Figure 6.8: *Meta-analysis (random effects model) – pooled study findings of pain tolerance (PTO) in response to thermal (heat) experimental pain, measured in degrees Celsius tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

The summary effect, the weighted standardised mean difference between cases and controls using a random effects model, is shown to be –4.168 (95% CI = -8.3 to -0.1), indicating significantly lower pain tolerance (and higher pain sensitivity) in patients in receipt of opioid therapy, compared with controls, in response to a hot noxious stimulus (p=0.046). The included studies are listed in **Figure 6.8** in chronological order of date of publication and it is shown that there is no pattern associated with findings over time. Substantial heterogeneity was identified

in study effects (I^2=99.19) [Q=246 (df=2); p<0.001; Tau^2=12.94 (SE=13.83; Variance=191; Tau=3.60)]. Heterogeneity was anticipated, hence the *a priori* decision to employ the use of a random effects model, and this will be examined further in subgroup/moderator analyses.

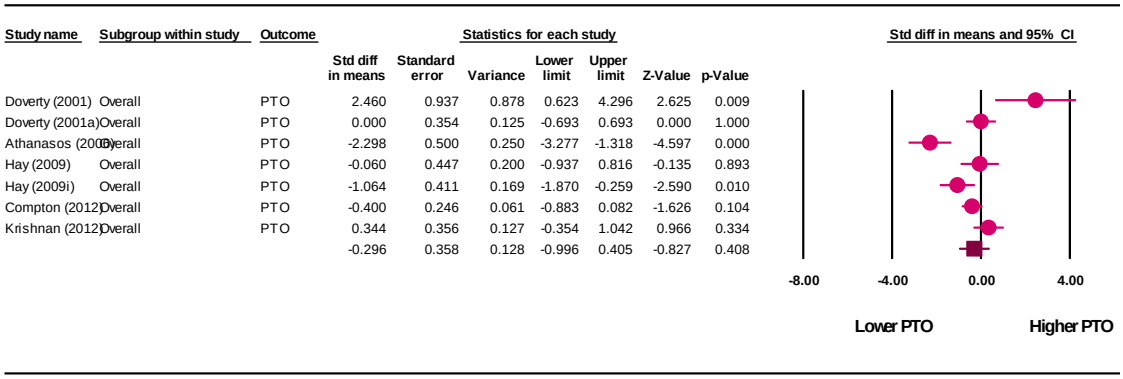


Figure 6.9: *Meta-analysis (random effects model) – pooled study findings of pain tolerance (PTO) in response to electrical experimental pain, measured in volts tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

The summary effect, the weighted standardised mean difference between cases and controls using a random effects model, is shown to be non-significant. The included studies are listed in ***Figure 6.9*** in chronological order of date of publication and it is shown that there is no pattern associated with findings over time.

Six of the seven study samples that underwent pain threshold assessment in response to noxious electrical stimuli also underwent pain threshold assessment in response to noxious thermal (cold) stimuli measured in seconds tolerated (Doverty, 2001; Doverty, 2001a; Athanasos, 2012; Hay, 2009 (opioid-dependent sample); Hay, 2009i (chronic pain sample); and Compton, 2012). The seventh sample (Krishnan, 2012) did not undergo thermal QST assessment of pain threshold. The pooled effect estimate of these six studies, in response to noxious thermal (cold) stimuli, is shown in ***Figure 6.9a***.

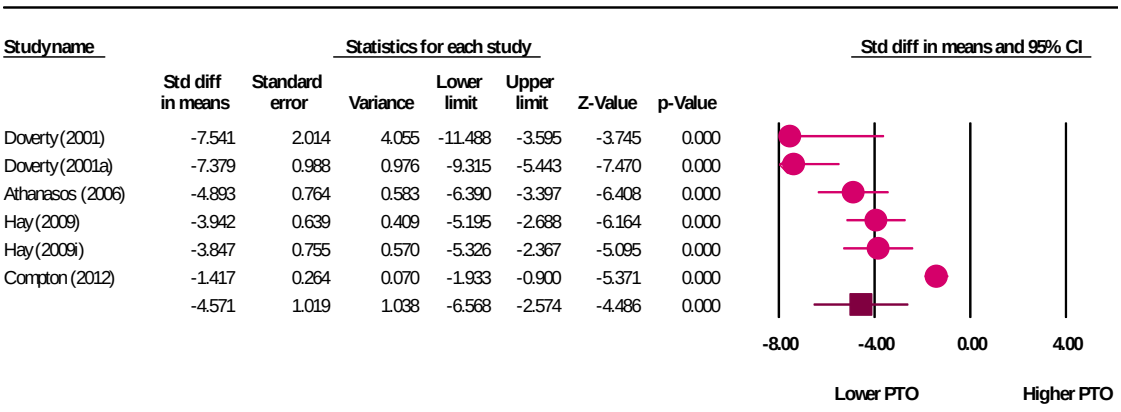


Figure 6.9a: *Meta-analysis (random effects model) – pooled study findings of pain tolerance (PTO) in response to thermal (cold) experimental pain, measured in seconds tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

Contrary to the findings of electrical experimental pain, the findings relating to thermal (cold) pain in the same samples were associated with significant group differences. The weighted standardised mean difference between cases and controls, using a random effects model, is shown to be -4.571 (95% CI = --6.568 to –2.574), indicating significantly lower pain threshold (and, consequently, higher pain sensitivity) in patients in receipt of opioid therapy, compared with controls, in response to a noxious cold stimulus ($p<0.001$).

6.3.4.3 Summary of main findings

These findings suggest that there is evidence of the development of opioid-induced hyperalgesia in humans but that this evidence is dependent upon the nature of the noxious stimulus (e.g. thermal versus electrical stimulation) and whether pain detection threshold or pain tolerance was used in the assessment procedure. The only significant summary effect for pain threshold was in response to noxious electrical stimuli; however, cases were associated with a higher mean threshold value than controls. All but one of these studies also assessed pain threshold in response to noxious thermal (cold) stimuli (measured in seconds to pain detection) and, conversely, a lower mean threshold value was found in cases compared with controls. There were significant summary effects for pain tolerance in the two thermal pain modalities. Cases, compared with controls, demonstrated significantly lower pain tolerance in response to noxious thermal (cold) stimuli (measured in seconds tolerated) and in response to noxious thermal (heat) stimuli (measured in degrees Celsius tolerated). Furthermore, in each of the two studies reporting response to noxious thermal (cold) stimuli, measured in degrees Celsius tolerated, the chronic pain group in receipt of opioids demonstrated significantly more

pain sensitivity compared with chronic pain groups not on opioids and with healthy controls. There was no significant group difference associated with noxious electrical stimuli; however, all but one of these studies also assessed pain tolerance in response to noxious thermal (cold) stimuli (measured in seconds tolerated) and cases were found to have a significantly lower tolerance value than controls.

6.3.5 Risk of bias across studies

Assessment of risk of publication bias was undertaken for articles in significant pain modalities: pain threshold in response to electrical stimuli; pain tolerance in response to cold stimuli measured in seconds; and pain tolerance in response to heat stimuli measured in degrees Celsius. In the absence of both heterogeneity and publication bias, 95% of points would lie within the guidelines drawn on the funnel plot. Findings are shown in ***Figures 6.10 - 6.12***.

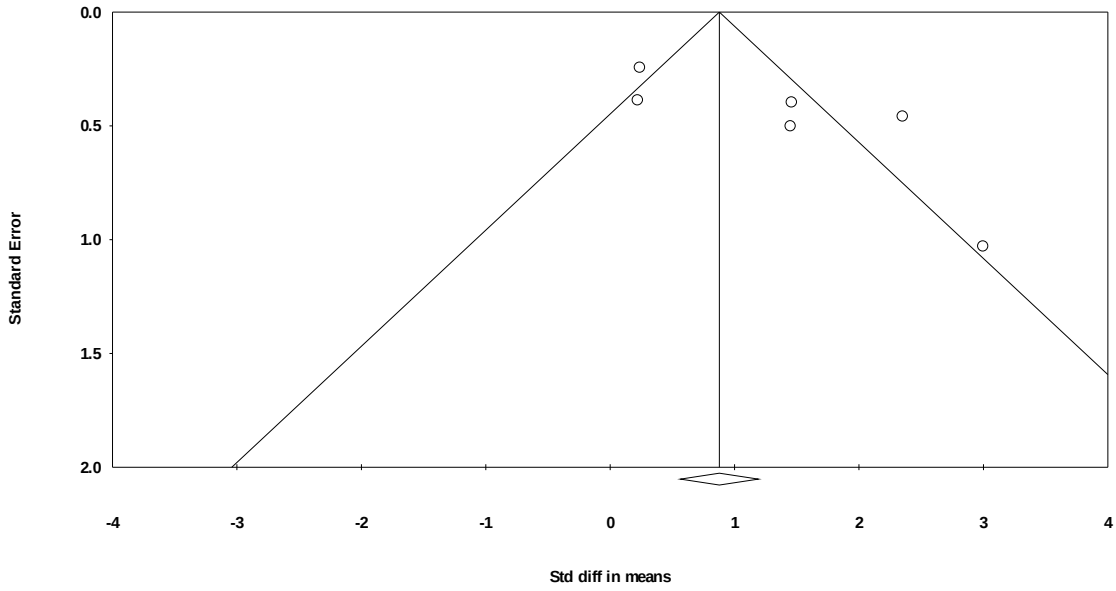


Figure 6.10: *Funnel plot of standard error of study effect by standardised difference in group means – for pain threshold (PTR) in response to electrical experimental pain, measured in volts tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

Figure 6.10 shows a distribution falling reasonably close to the plot guidelines. The distribution suggests little publication bias, confirmed by the Egger regression intercept (t=2.44; df=4; p=0.071). The previously-reported heterogeneity is, however, evident in the funnel plot – since some of the study points fall beyond the 'funnel' guidelines – and was therefore explored using subgroup/moderator analyses.

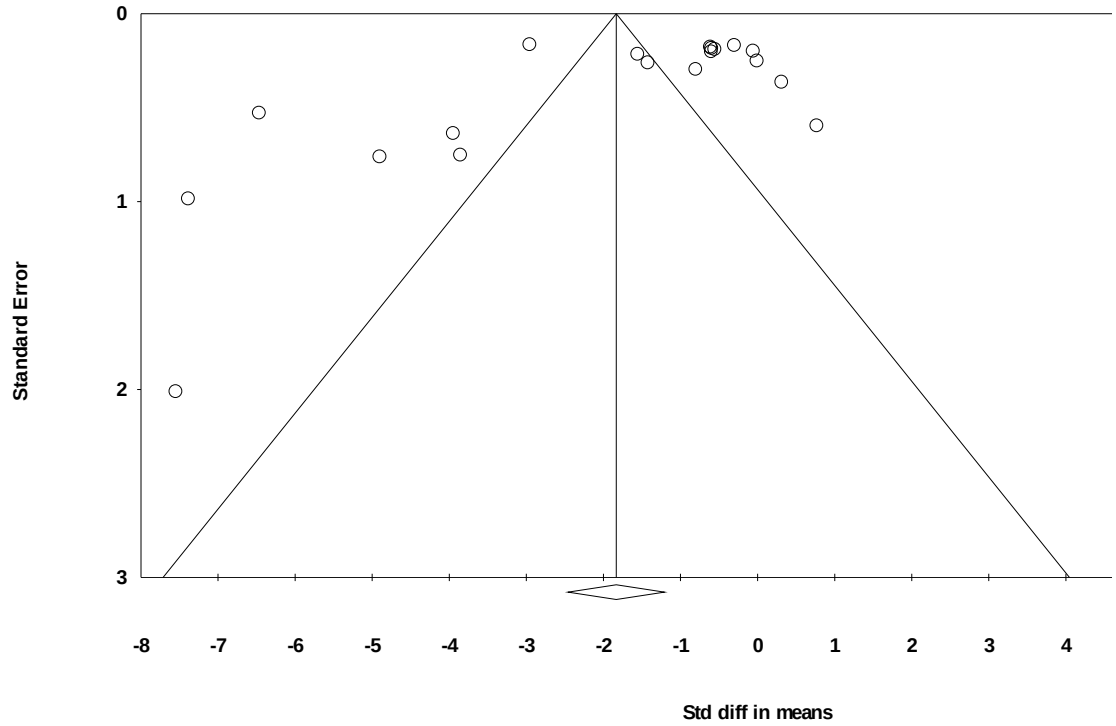


Figure 6.11: *Funnel plot of standard error of study effect by standardised difference in group means – for pain tolerance (PTO) in response to thermal (cold) experimental pain, measured in seconds tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

Figure 6.11 shows a distribution whereby many individual studies with relatively high sample sizes (shown towards the top of the plot) fall beyond the anticipated distribution range – both to the left of centre (indicating effect sizes lower than the mean) and to the right of centre (indicating effect sizes higher than the mean). There was, however, no significant publication bias, confirmed by the Egger regression intercept (t=1.95; df=17; p=0.068). The previously-reported heterogeneity is, however, evident in the funnel plot – since most of the study points fall beyond the 'funnel' guidelines – and was therefore explored using subgroup/moderator analyses.

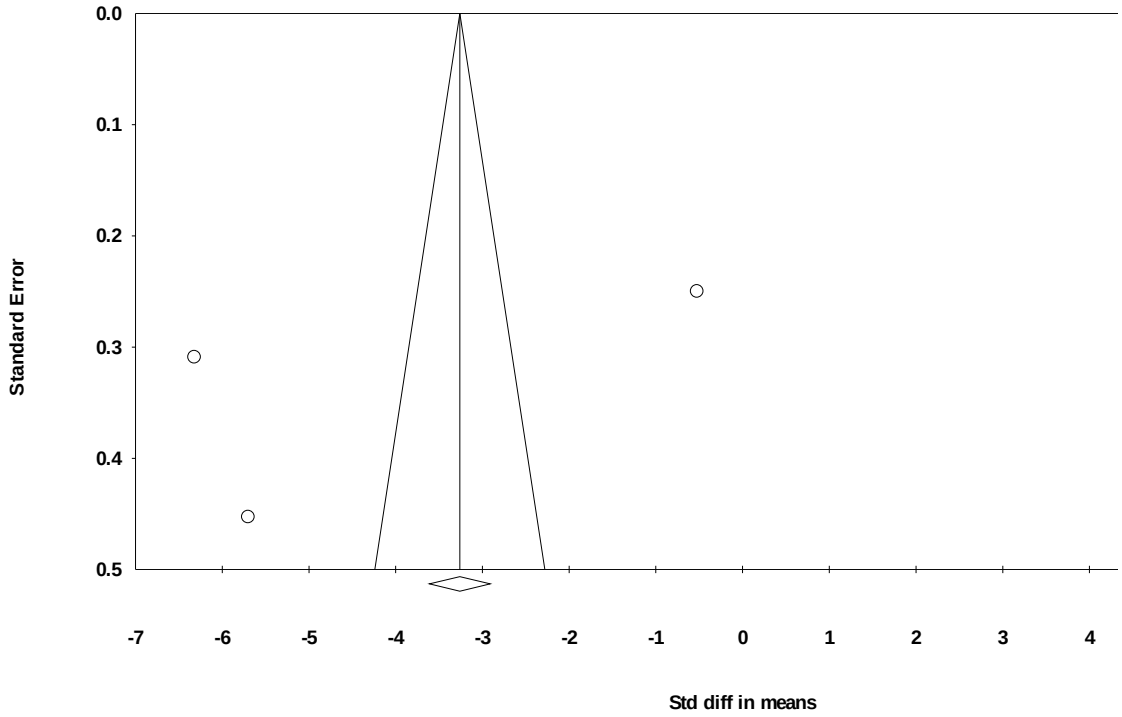


Figure 6.12: *Funnel plot of standard error of study effect by standardised difference in group means – for pain tolerance (PTO) in response to thermal (heat) experimental pain, measured in degrees Celsius tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

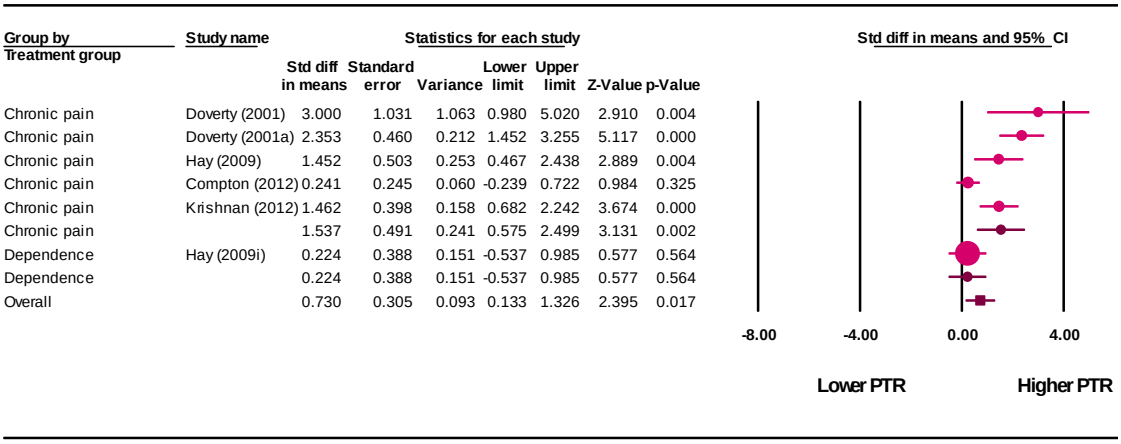
Figure 6.12 shows a fairly symmetrical distribution; however, the number of samples is small and, in consequence, statistical power may be limited. The relatively symmetrical distribution suggests little publication bias, confirmed by the Egger regression intercept (t=0.97; df=1; p=0.510). The previously-reported heterogeneity is, however, evident in the funnel plot – since the study points fall far from the 'funnel' guidelines – and was therefore explored using subgroup/moderator analyses.

6.3.6 Additional analyses

Subgroup/moderator analyses were undertaken, using meta-regression, for pain modalities associated with significant standardised mean differences between cases and controls (PTR in response to noxious electrical stimuli; PTO in response to thermal (cold) noxious stimuli measured in seconds tolerated; and PTO in response to thermal (heat) noxious stimuli measured in degrees Celsius tolerated). Meta-regression was run separately for three subgroup variables (treatment group, NMDA receptor antagonism and opioid dose) and one moderator variable (quality assessment of articles). Where significant differences in group summary effects were reported, the appropriate subgroup or moderator variable were entered into a regression model

in an effort to explain the overall variance in study effects. Where models significantly explained some of the heterogeneity in study effects, finding were reported.

6.3.6.1 Subgroup/moderator analyses for overall heterogeneity of study effects: Pain threshold (PTR) in response to noxious electrical stimuli, measured in volts tolerated



Group by Treatment group	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Chronic pain	Doverty (2001)	3.000	1.031	1.063	0.980	5.020	2.910	0.004
Chronic pain	Doverty (2001a)	2.353	0.460	0.212	1.452	3.255	5.117	0.000
Chronic pain	Hay (2009)	1.452	0.503	0.253	0.467	2.438	2.889	0.004
Chronic pain	Compton (2012)	0.241	0.245	0.060	-0.239	0.722	0.984	0.325
Chronic pain	Krishnan (2012)	1.462	0.398	0.158	0.682	2.242	3.674	0.000
Chronic pain		1.537	0.491	0.241	0.575	2.499	3.131	0.002
Dependence	Hay (2009i)	0.224	0.388	0.151	-0.537	0.985	0.577	0.564
Dependence		0.224	0.388	0.151	-0.537	0.985	0.577	0.564
Overall		0.730	0.305	0.093	0.133	1.326	2.395	0.017

Figure 6.13: *Meta-analysis (random effects model) of whether patients were treated for chronic pain or opioid dependence – pooled study findings of pain threshold (PTR) in response to electrical experimental pain, measured in volts tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

As ***Figure 6.13*** shows, pooled effect estimates of pain threshold to noxious electrical stimuli differed significantly by treatment group ($p<0.001$). There was a significantly greater difference between cases and controls in studies assessing patients with chronic pain (+1.537; k=5) compared with studies assessing patients with opioid dependence (+0.224; k=1). The differences were, however, in the opposite direction to the hypothesis with cases demonstrating higher threshold (and, consequently, lower sensitivity) than controls. In consequence, the greater difference between cases and controls in patients with chronic pain reflected greater pain sensitivity in opioid-dependent patients than in patients with chronic pain. Meta-regression generated a non-significant model.

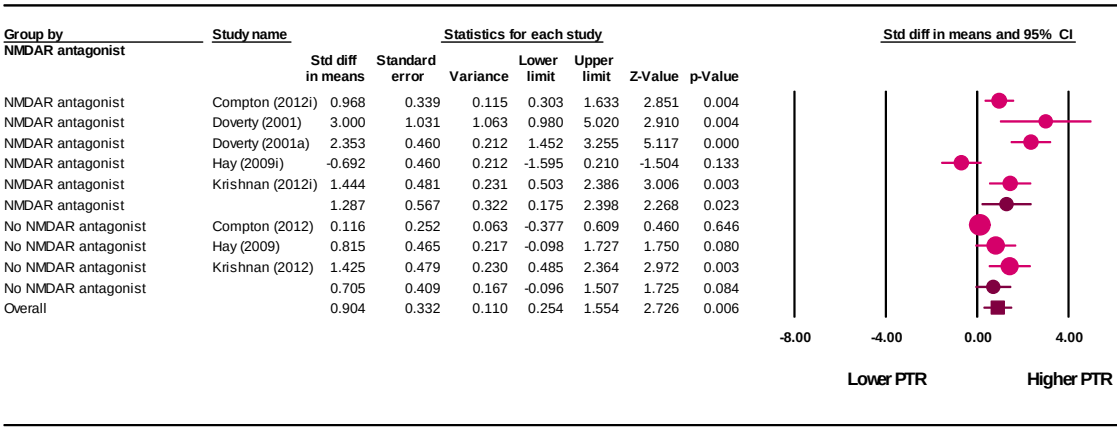


Figure 6.14: *Meta-analysis (random effects model) of whether patients were or were not treated with an opioid-based NMDA receptor antagonist – pooled study findings of pain threshold (PTR) in response to electrical experimental pain, measured in volts tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

As ***Figure 6.14*** shows, pooled effect estimates of pain threshold to noxious electrical stimuli differed significantly by NMDA receptor antagonist treatment group (p=0.006). There was a significantly greater difference between cases and controls in studies where NMDA receptor antagonists were used (+1.287; k=5) compared with opioids with no NMDA receptor antagonist properties (+0.705; k=3). The differences were, however, in the opposite direction to the hypothesis with cases demonstrating higher threshold (and, consequently, lower sensitivity) than controls. In consequence, the greater difference between cases and controls where NMDA receptor antagonists were used indicated reflected greater pain sensitivity in these groups. It should be noted, however, that most of the studies reporting use of NMDA receptor antagonists were reporting on methadone-maintained opioid dependent populations. Meta-regression generated a non-significant model.

The pooled effect estimates of pain threshold to noxious electrical stimuli by opioid dose were computed. Whilst the standardised mean difference between cases and controls increased slightly as a function of increasing opioid dose, the effect was non-significant and, in consequence, did not account for variance in overall study effects.

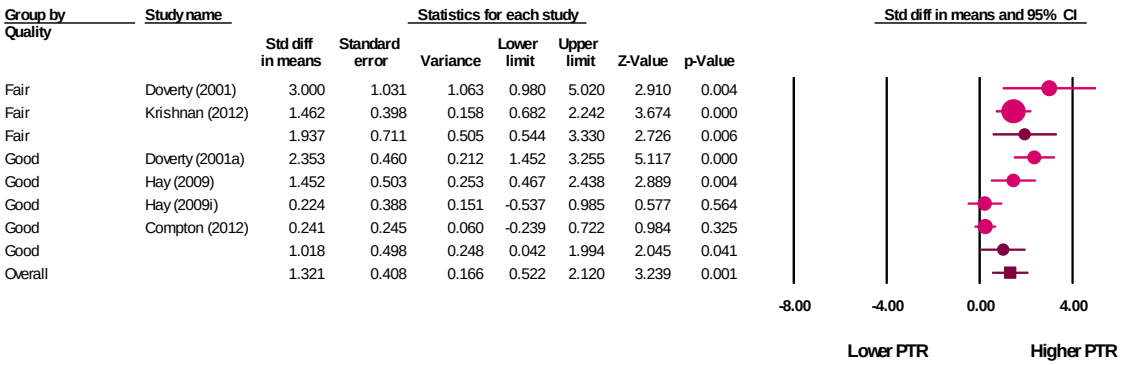
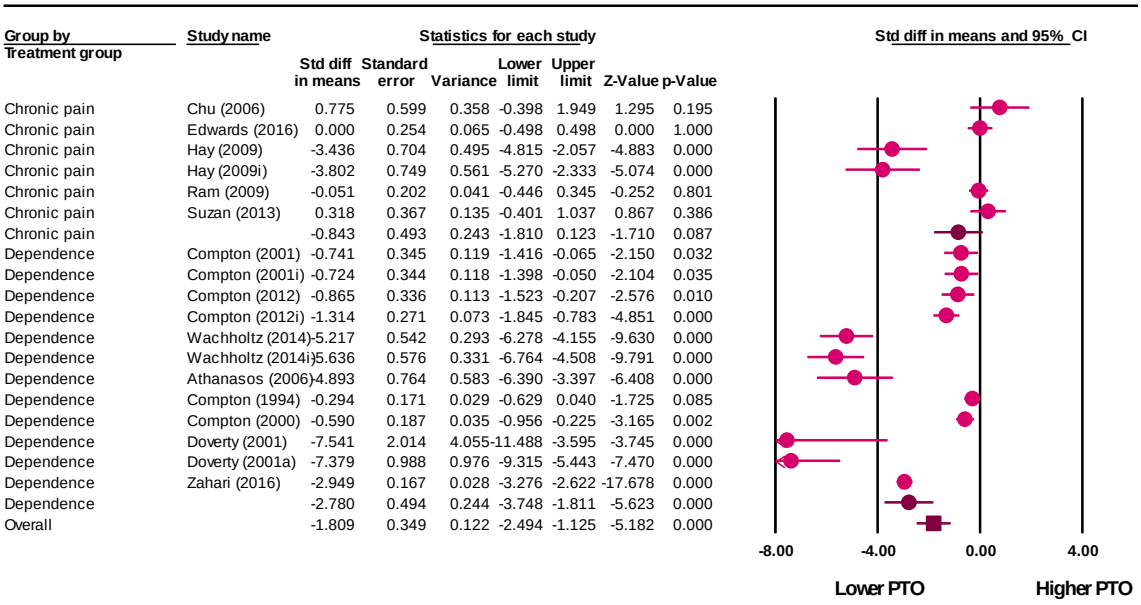


Figure 6.15: *Meta-analysis (random effects model) of study quality ('fair' or 'good') – pooled study findings of pain threshold (PTR) in response to electrical experimental pain, measured in volts tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

As ***Figure 6.15*** shows, pooled effect estimates of pain threshold to noxious electrical stimuli differed significantly by study quality (p=0.001). There was a significantly greater difference between cases and controls in studies reported to be of 'fair' quality (+1.937; k=2) compared with studies to be reported of 'good' quality (+1.018; k=4). The differences were, however, in the opposite direction to the hypothesis with cases demonstrating higher threshold (and, consequently, lower sensitivity) than controls. In consequence, the greater difference between cases and controls in studies identified as being of 'fair' quality reflected lower pain sensitivity in these groups compared with studies identified as being of 'good' quality. Meta-regression generated a non-significant model.

6.3.6.2 Subgroup/moderator analyses for overall heterogeneity of study effects: Pain tolerance (PTO) in response to noxious thermal (cold) stimuli, measured in seconds tolerated



Group by Treatment group	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Chronic pain	Chu (2006)	0.775	0.599	0.358	-0.398	1.949	1.295	0.195
Chronic pain	Edwards (2016)	0.000	0.254	0.065	-0.498	0.498	0.000	1.000
Chronic pain	Hay (2009)	-3.436	0.704	0.495	-4.815	-2.057	-4.883	0.000
Chronic pain	Hay (2009i)	-3.802	0.749	0.561	-5.270	-2.333	-5.074	0.000
Chronic pain	Ram (2009)	-0.051	0.202	0.041	-0.446	0.345	-0.252	0.801
Chronic pain	Suzan (2013)	0.318	0.367	0.135	-0.401	1.037	0.867	0.386
Chronic pain		-0.843	0.493	0.243	-1.810	0.123	-1.710	0.087
Dependence	Compton (2001)	-0.741	0.345	0.119	-1.416	-0.065	-2.150	0.032
Dependence	Compton (2001i)	-0.724	0.344	0.118	-1.398	-0.050	-2.104	0.035
Dependence	Compton (2012)	-0.865	0.336	0.113	-1.523	-0.207	-2.576	0.010
Dependence	Compton (2012i)	-1.314	0.271	0.073	-1.845	-0.783	-4.851	0.000
Dependence	Wachholtz (2014)	-5.217	0.542	0.293	-6.278	-4.155	-9.630	0.000
Dependence	Wachholtz (2014i)	-5.636	0.576	0.331	-6.764	-4.508	-9.791	0.000
Dependence	Athanasos (2006)	-4.893	0.764	0.583	-6.390	-3.397	-6.408	0.000
Dependence	Compton (1994)	-0.294	0.171	0.029	-0.629	0.040	-1.725	0.085
Dependence	Compton (2000)	-0.590	0.187	0.035	-0.956	-0.225	-3.165	0.002
Dependence	Doverty (2001)	-7.541	2.014	4.055	-11.488	-3.595	-3.745	0.000
Dependence	Doverty (2001a)	-7.379	0.988	0.976	-9.315	-5.443	-7.470	0.000
Dependence	Zahari (2016)	-2.949	0.167	0.028	-3.276	-2.622	-17.678	0.000
Dependence		-2.780	0.494	0.244	-3.748	-1.811	-5.623	0.000
Overall		-1.809	0.349	0.122	-2.494	-1.125	-5.182	0.000

Figure 6.16: *Meta-analysis (random effects model) of whether patients were treated for chronic pain or opioid dependence – pooled study findings of pain tolerance (PTO) in response to thermal (cold) experimental pain, measured in seconds tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

As ***Figure 6.16*** shows, the pooled effect estimates of pain tolerance in response to cold noxious stimuli differed significantly by treatment group ($p<0.001$). Studies where patients were treated for chronic pain ($k=6$) generated a pooled standardised mean difference between cases and controls of -0.843 ($p=0.087$). Studies where patients were treated for opioid dependence ($k=12$) generated a significantly higher pooled standardised mean difference between cases and controls of -2.780 ($p<0.001$). This indicates that, in both treatment groups, cases had lower pain tolerance (and, consequently, higher pain sensitivity) than controls and that pain sensitivity was relatively higher in patients treated for opioid dependence compared with chronic pain. The meta-regression model was statistically significant ($Q=5.26$; $df=1$; $p=0.022$) and the results are shown in ***Table 6.3***.

Table 6.3: *Random effects (DerSimonian-Laird) meta-regression of the standardised difference in means on whether patients were treated for opioid dependence or chronic pain using a Z-distribution*

Covariate	Coefficient	SE	95% lower	95% upper	Z value	p value
Intercept	-0.9182	0.6472	-2.1867	0.3503	-1.42	0.156
Opioid dep.	-1.8289	0.7974	-3.3918	-0.2661	-2.29	0.022

Patients treated for opioid dependence are associated with almost twice the difference between cases and controls as compared with patients treated for chronic pain. The coefficient is negative, suggesting that, compared with chronic pain, patients treated for opioid dependence were significantly associated with lower pain tolerance and, consequently, with elevated pain sensitivity. The meta-regression showed that the inclusion of this subgroup variable in the regression model explained 6% of the overall variance in study effects (R^2=0.06).

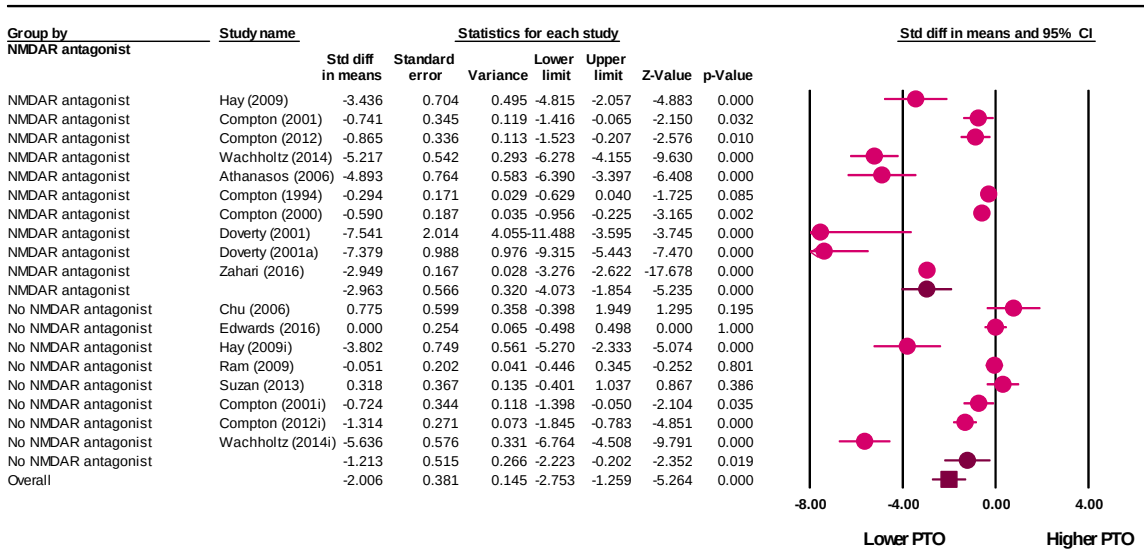


Figure 6.17: *Meta-analysis (random effects model) of whether or not the opioid was an NMDA receptor antagonist – pooled study findings of pain tolerance (PTO) in response to thermal (cold) experimental pain, measured in seconds tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

As ***Figure 6.17*** shows, the pooled effect estimates of pain tolerance in response to cold noxious stimuli differed significantly by NMDA receptor antagonist treatment group (p<0.001). Studies using an NMDA receptor antagonist (k=10) generated a pooled standardised difference between cases and controls of -2.963 (p<0.001). Studies using a non-NMDA receptor antagonist (k=8)

generated a pooled standardised difference between cases and controls of -1.213 (p=0.019). These findings indicated higher pain sensitivity in NMDA receptor antagonist-treated groups. It should be noted, however, that most of the studies reporting use of NMDA receptor antagonists were reporting on methadone-maintained opioid dependent populations. The meta-regression model was statistically significant (Q=4.69; df=1; p=0.030) and the results are shown in ***Table 6.4***.

Table 6.4: *Random effects (DerSimonian-Laird) meta-regression of the standardised difference in means on whether or not the opioid used in treatment was an NMDA receptor antagonist using a Z-distribution*

Covariate	**Coefficient**	**SE**	**95% lower**	**95% upper**	**Z value**	**p value**
Intercept	-2.9298	0.5355	-3.9793	-1.8802	-5.47	<0.001
NMDAR antag.	-1.7005	0.7849	-3.2389	-0.1622	-2.17	0.030

The use of NMDA receptor antagonists is associated with almost twice the difference between cases and controls as compared with the use of non-NMDA receptor antagonists. The coefficient is negative, suggesting that patients in receipt of NMDA receptor antagonists were significantly associated with lower pain tolerance and, consequently, with elevated pain sensitivity. The meta-regression showed that the inclusion of this subgroup variable in the regression model explained less than 1% of the overall variance in study effects.

Meta-regression of the standardised difference in means on mean morphine-equivalent opioid dose was significant (Q=6.25; df=1; p=0.012); the regression line is shown in ***Figure 6.18*** and the findings are shown in ***Table 6.5***.

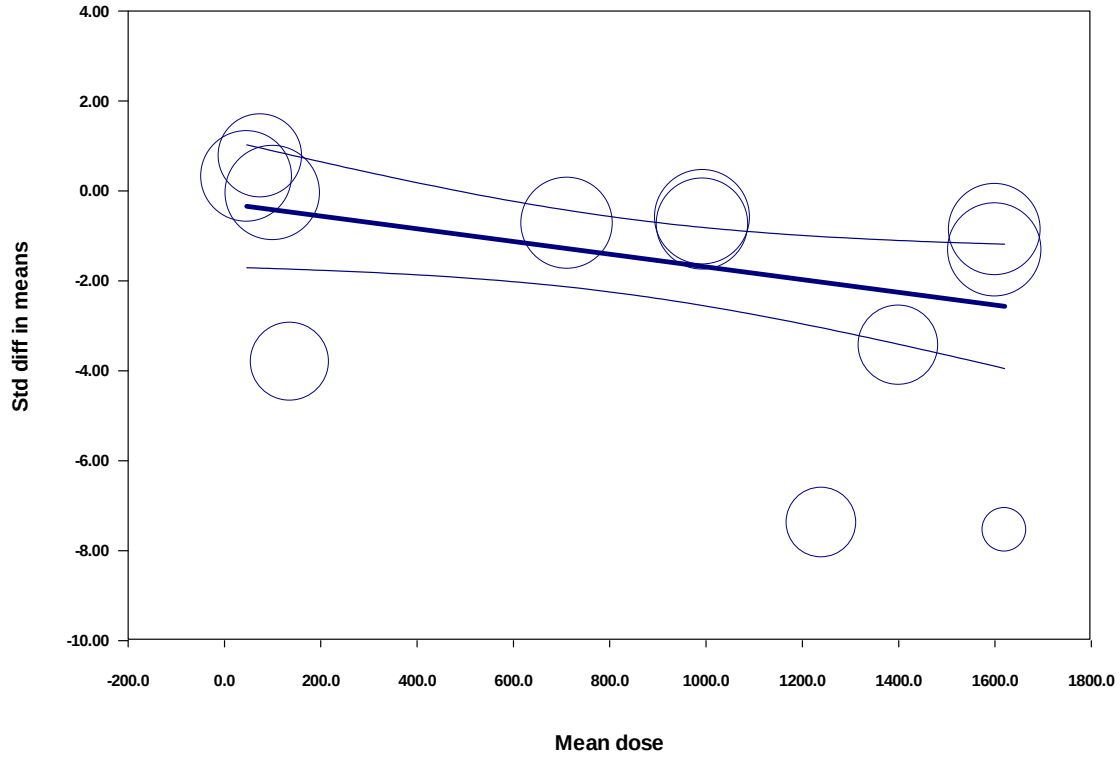


Figure 6.18: *Regression of standardised difference in means on mean morphine-equivalence opioid dose*

Table 6.5: *Random effects (DerSimonian-Laird) meta-regression of the standardised difference in means on mean morphine-equivalent opioid dose using a Z-distribution*

Covariate	Coefficient	SE	95% lower	95% upper	Z value	p value
Intercept	-0.2761	0.5795	-1.4119	0.8598	-0.48	0.634
DSM-IV	-0.0014	0.0006	-0.0025	-0.0003	-2.50	0.012

The standardised differences in mean PTO between cases and controls decreased significantly in association with increased mean morphine-equivalent opioid dose, suggesting that increased doses were associated with increased tolerance and, consequently, decreased pain sensitivity. The meta-regression showed that the inclusion of this subgroup variable in the regression model explained 9% of the overall variance in study effects (R^2=0.09).

Group by Quality	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Fair	Athanasos (2006)	-4.893	0.764	0.583	-6.390	-3.397	-6.408	0.000
Fair	Chu (2006)	0.775	0.599	0.358	-0.398	1.949	1.295	0.195
Fair	Compton (2001)	-0.795	0.299	0.089	-1.380	-0.210	-2.662	0.008
Fair	Doverty (2001)	-7.541	2.014	4.055	-11.488	-3.595	-3.745	0.000
Fair	Suzan (2013)	0.318	0.367	0.135	-0.401	1.037	0.867	0.386
Fair		-1.777	0.903	0.816	-3.548	-0.007	-1.968	0.049
Good	Compton (1994)	-0.294	0.171	0.029	-0.629	0.040	-1.725	0.085
Good	Compton (2000)	-0.590	0.187	0.035	-0.956	-0.225	-3.165	0.002
Good	Compton (2012)	-1.417	0.264	0.070	-1.933	-0.900	-5.371	0.000
Good	Doverty (2001a)	-7.379	0.988	0.976	-9.315	-5.443	-7.470	0.000
Good	Edwards (2016)	0.000	0.254	0.065	-0.498	0.498	0.000	1.000
Good	Eisenberg (2007)	-0.549	0.192	0.037	-0.925	-0.173	-2.862	0.004
Good	Hay (2009)	-3.942	0.639	0.409	-5.195	-2.688	-6.164	0.000
Good	Hay (2009i)	-3.847	0.755	0.570	-5.326	-2.367	-5.095	0.000
Good	Ho (2011)	-1.548	0.218	0.048	-1.975	-1.121	-7.103	0.000
Good	Pud (2006)	-0.605	0.180	0.032	-0.957	-0.252	-3.361	0.001
Good	Ram (2009)	-0.051	0.202	0.041	-0.446	0.345	-0.252	0.801
Good	Treister (2012)	-0.594	0.204	0.042	-0.994	-0.193	-2.906	0.004
Good	Wachholtz (2014)	-6.458	0.531	0.282	-7.499	-5.418	-12.168	0.000
Good	Zahari (2016)	-2.949	0.167	0.028	-3.276	-2.622	-17.678	0.000
Good		-1.920	0.357	0.127	-2.619	-1.220	-5.379	0.000
Overall		-1.901	0.332	0.110	-2.551	-1.250	-5.725	0.000

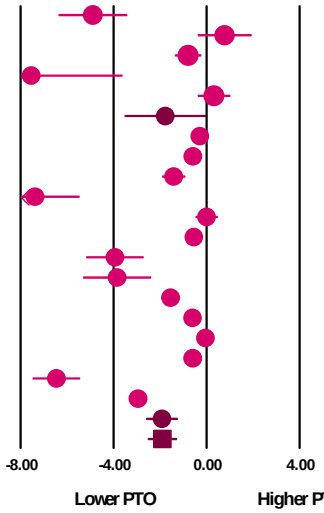


Figure 6.19: *Meta-analysis (random effects model) of study quality ('fair' or 'good') – pooled study findings of pain tolerance (PTO) in response to thermal (cold) experimental pain, measured in seconds tolerated, at a non-painful site in patients in receipt of chronic opioid analgesic therapy or opioid replacement therapy for the treatment of opioid dependence.*

As ***Figure 6.19*** shows, pooled effect estimates of pain threshold to noxious thermal (cold) stimuli differed significantly by study quality ($p<0.001$). There was a significantly greater difference between cases and controls in studies reported to be of 'good' quality (-1.920; k=14) compared with studies to be reported of 'fair' quality (-1.777; k=5). These findings indicated lower pain sensitivity in studies reported to be of 'fair' quality compared to studies reported to be of 'good' quality. Meta-regression generated a non-significant model.

6.3.6.3 Subgroup/moderator analyses for overall heterogeneity of study effects: Pain tolerance (PTO) in response to noxious thermal (heat) stimuli, measured in degrees Celsius tolerated

All studies involved patients treated for chronic pain, none used opioids with NMDA receptor antagonist properties and all were reported to be of 'good' quality. Mean opioid dose was reported in two of the three studies and this was insufficient data to generate a meta-regression model.

6.4 Summary of evidence

The primary objective of the current review was to undertake a systematic review and meta-analysis of studies examining evidence for OIH in humans following chronic opioid exposure. Electronic and manual searches, including grey literature searches, were undertaken, and 6167 articles were identified. A total of 1831 duplicates were removed resulting in 4336 articles available for eligibility review. Examination of titles and abstracts determined that 3556 articles were ineligible and, in consequence, 780 articles remained eligible for full text review. A total of 754 articles were excluded during full text review resulting in a total of 26 studies retained for inclusion in the meta-analysis. These 26 studies included 2706 participants.

Pooled summary effect estimates were generated using the random effects (DerSimonian-Laird method) model. Individual studies were weighted in accordance with the principle of inverse variance and, since a random effects model was applied, this included between-study variance in addition to within-study variance. Findings suggested that there was evidence of OIH following chronic opioid exposure in response to noxious thermal stimuli assessed by pain tolerance. There was, however, little evidence to suggest that OIH can be identified using assessments of pain detection threshold. Cases, compared with controls, demonstrated significantly lower pain tolerance (and, consequently higher pain sensitivity) in response to noxious thermal (cold) stimuli (measured in seconds tolerated) and in response to noxious thermal (heat) stimuli (measured in degrees Celsius tolerated). Furthermore, in each of the two studies reporting response to noxious thermal (cold) stimuli, measured in degrees Celsius tolerated, the chronic pain group in receipt of opioids demonstrated significantly more pain sensitivity compared with chronic pain groups not on opioids and with healthy controls. There was no significant group difference associated with noxious electrical stimuli; however, all but one of these studies also assessed pain threshold and tolerance in response to noxious thermal (cold) stimuli (measured in seconds tolerated) and cases were found to have a significantly lower threshold and tolerance values than controls. There was no significant publication bias but substantial heterogeneity in study effects was identified.

In an effort to examine the secondary hypotheses and to explain the substantial heterogeneity found in these meta-analyses, a number of subgroup/moderator analyses were undertaken. Where significant, the relevant subgroup or moderator variable was entered in a meta-regression (DerSimonian-Laird method). Group differences in summary effects were computed where there were significant differences between cases and controls and there were sufficient data to undertake subgroup/moderator analyses: pain threshold in response to noxious electrical stimuli; and pain tolerance in response to noxious thermal (cold) stimuli (measured in

seconds tolerated. Subgroup/moderator analyses were not feasible for pain tolerance in response to noxious thermal (heat) stimuli measured in degrees Celsius since all studies: assessed patients with chronic pain; used non-NMDA receptor antagonists; and were identified as being of 'good' quality. Furthermore, only two of the three studies reported opioid treatment dose and this was insufficient to generate a meta-regression model. OIH was significantly more evident in opioid-dependent patients than in patients treated for chronic pain in both experimental pain modalities and this finding accounted for 6% of variance in study effects in the thermal (cold) pain modality. OIH was significantly more evident in samples treated with NMDA receptor antagonists but this group difference accounted for less than 1% of variance in study effects in both modalities. There was no effect of opioid treatment dose on OIH in response to noxious electrical stimuli but higher doses were significantly associated with decreased pain sensitivity in response to thermal (cold) stimuli. This finding did not account for any variance in study effects. In both modalities, studies rated as 'good' quality were significantly associated with relatively more conservative study effects but this did not account for any variance in study effects.

In summary, there was evidence of opioid-induced hyperalgesia in response to thermally-induced (hot and cold) experimental pain, but not in response to noxious electrical stimuli. This finding was dependent upon the metric used to assess hyperalgesia – strong evidence was associated with measures of pain tolerance but not with measures of pain threshold.

6.5 Limitations

The principal limitation of the current review was that, due to pragmatic considerations, included articles were restricted to those written in English. One further limitation is that only 25% of included articles were assessed by a second reviewer. Whilst this is conventional practice, reviews could be strengthened further by all included articles being assessed by a second reviewer.

Chapter 7

Discussion: The clinical implications of comorbid chronic pain in treatment-seeking, opioid-dependent patients

The overarching aim of the present thesis was to explore the clinical challenges associated with treatment-seeking, opioid-dependent patients with comorbid chronic pain. Using routinely-available NHS data pertaining to patients in receipt of opioid replacement therapy (ORT) for the treatment of opioid dependence, the clinical and treatment characteristics of this 'comorbid' group were compared with those of treatment-seeking opioid-dependent patients with no pain. Long-term ORT treatment outcomes (substance use and general health) were also compared in these two groups over a 5-year follow-up period. Furthermore, in an attempt to further discern the impact of the dynamic relationship between chronic pain and opioid dependence, clinical associations with the patient-attributed direction of the causal relationship between these two conditions were examined. Using systematic review and meta-analytical techniques, two further research questions were examined. First, the pooled incidence of iatrogenic dependence on opioids was computed. Secondly, evidence for the development of opioid-induced hyperalgesia in clinical populations was examined.

The first key finding was that the comorbid group presented as a clinically-distinct group, compared with ORT patients with no pain, and was associated with a range of more complex treatment challenges. Mortality during the follow-up period was significantly higher in the comorbid pain group, with more than 10% of the group having died during that period. Whilst intentional self-harm (i.e. suicide) was a prominent cause of death in ORT patients with no pain, medical morbidity was a prominent cause of death in the comorbid pain group. Significantly elevated use of cannabinoids and benzodiazepines was evident in the comorbid pain group at study inception and this problem continued during the follow-up period. Conversely, a significantly lower proportion of the comorbid pain group was associated with illicit heroin use at study inception but there were no group differences concerning overall illicit opioid use at study inception or during the follow-up period. Illicit heroin use, specifically, was not assessed during the follow-up period. Patients in the comorbid pain group reported significantly more symptoms of medical morbidity at study inception; however, many of the symptoms assessed using the standardised instruments may reflect aspects of pain syndromes. Assessment of

prescription medication and inpatient treatment for other severe and/or chronic medical morbidities did not reveal substantial group differences at study inception or during the follow-up period. In contrast, however, the comorbid pain group was significantly associated with elevated psychiatric morbidity at both study inception and during the follow-up period. This was characterised by anxiety-related disorders, mood disorders and problems with general life functioning. The comorbid pain group was, however, associated with significantly less inpatient treatment for psychoactive substance use and alcohol dependence disorders.

The second key finding was that, within the comorbid pain group, there was evidence to suggest that the patient-attributed direction of the causal relationship between chronic pain and opioid dependence may identify subgroups that are associated with differing clinical characteristics and treatment challenges. Illicit use of any substances was significantly higher in the group reporting that opioid dependence caused chronic pain. This was characterised by an elevated proportion of the group reporting use of methadone, opioid analgesics and cannabinoids, and reporting more frequent use of methadone and heroin. Conversely, of those that reported illicit use of opioid analgesics, more frequent use was significantly associated with the group reporting that chronic pain caused opioid dependence. There were very few group differences concerning physical health and additional medical morbidity. The group reporting that opioid dependence caused chronic pain was significantly associated with a higher general physical health score (problem-scored, therefore, indicative of poorer physical health) and more inpatient admissions and total nights spent in inpatient treatment facilities during the follow-up period. Also, a significantly higher proportion of the group reporting that opioid dependence caused chronic pain was associated with psychiatric 'caseness'. This was characterised by significantly elevated scores (indicative of more severe symptom severity) on all of the GHQ-28 subscales (social dysfunction, somatic symptoms and anxiety/insomnia) and three of the four CORE subscales (problems/symptoms, life functioning and risk/harm). This group was also significantly associated with more inpatient admissions; however, conversely, the group reporting that chronic pain caused opioid dependence was significantly associated with a higher mean number of nights spent in inpatient facilities during the follow-up period. There was no significant group difference concerning the proportions in receipt of opioid analgesics; however, a significantly higher prescribed dose was recorded in the group reporting that chronic pain caused opioid dependence. There were no significant group differences concerning ORT or benzodiazepine prescribing regimens.

Physical health and pain symptoms were predictive of initiation and continuation of illicit opioid use solely in the group reporting that chronic pain caused opioid dependence. Patient

perceptions of their pain problems having been taken seriously by the treating physician, however, were protective of initiation of illicit opioid use in this group during the follow-up period. In the group reporting that opioid dependence caused chronic pain, increasing duration of pain at study inception was significantly protective of continued benzodiazepine use and patient perceptions of their pain problems having been taken seriously by the treating physician were protective of initiation of cannabinoid use. Pain interference on daily activities was associated with significant risk of continuation of illicit cannabinoid use in this group. A number of psychiatric characteristics were significantly predictive of risk for initiation of opioid use during the follow-up period in the group reporting that chronic pain caused opioid dependence (psychiatric 'caseness', severe depression, anxiety/insomnia, somatic symptoms and social dysfunction). Conversely, risk for continuation of illicit opioid use was associated with psychiatric 'caseness' in the group reporting that opioid dependence caused chronic pain. Similar to the findings associated with initiation of illicit opioid use, all significant findings associated with initiation of nonmedical benzodiazepine use were found solely in relation to the group reporting that chronic pain caused opioid dependence. Elevated risk in this group was associated with psychiatric 'caseness'; severe depression; anxiety/insomnia; somatic symptoms; social dysfunction; and social phobia. A significant predictive association was also found between psychiatric 'caseness' and initiation of cannabinoid use in this group. During the follow-up period, increasing opioid doses were associated with elevated risk of illicit or nonmedical substance use. Significant risk of initiation of opioid use was found in the group reporting that chronic pain caused opioid dependence. Conversely, significant risk of continuation of benzodiazepine use was found in the group reporting that opioid dependence caused chronic pain. Significant risk of initiation of cannabinoid use was found in both groups and significant risk of continuation was found in the group reporting that opioid dependence caused chronic pain.

The third key finding was that, using systematic review and meta-analytical techniques (k=12; n=310,408), incidence of iatrogenic dependence on opioids was found to be less than 5%. Meta-regression models revealed that prospective studies were associated with the lowest incidence (1.7%) followed by cross-sectional studies (4.7%), and that pre- post- (also known as 'before-and-after') studies were associated with the highest incidence (10.7%). Studies identified as being of 'good' quality generated a significantly lower incidence (3.1%) compared with studies identified as being of 'fair' quality (15.1%). Studies using ICD-9 diagnostic criteria were associated with a significantly lower incidence (1.3%) than studies that used DSM-IV criteria (11.3%). Studies limiting inclusion to patients that underwent chronic exposure to opioid analgesics (>3 months) were associated with a significantly lower incidence (2.3%) than studies

that included patients of varied exposure (10.7%). Studies that used only 'strong' opioids generated a significantly lower incidence (0.7%) than studies that used only 'weak' opioids (5.5%) or a mix of 'strong' and 'weak' opioids (6.1%).

The fourth key finding was that, using systematic review and meta-analytical techniques (k=26; n=2706), there was some evidence of opioid-induced hyperalgesia in clinical populations. The evidence was specific to noxious thermal stimuli and not to noxious electrical stimuli and, furthermore, it was specific to pain tolerance metrics and not pain threshold metrics. The only significant summary effect for pain threshold was in response to noxious electrical stimuli; however, the opioid-treated group was significantly more pain tolerant than controls. Six of these seven studies also assessed responses to the cold pressor test and, contrary to responses to noxious electrical stimuli, findings showed significantly reduced pain tolerance in the opioid-treated group compared with controls. There was evidence of opioid-induced hyperalgesia, using pain tolerance metrics, in response to noxious cold stimuli (measured in seconds tolerated) and in response to noxious heat stimuli (measured in temperature tolerated), whereby pain tolerance was significantly reduced in opioid-treated groups compared with controls.

7.1 Clinical implications of comorbid chronic pain in treatment-seeking, opioid-dependent populations

7.1.1 Prevalence of chronic pain in ORT programme

The prevalence of chronic pain in this ORT clinical population was found to be 53%. Prevalence reports vary in the literature, ranging from around 37% (Rosenblum *et al.*, 2003) to around 61% (Jamison *et al.*, 2000). The current finding sits squarely within the reported range and are very similar to the findings of Dhingra and colleagues (2013) who reported prevalence of around 49%. The diagnostic threshold for chronicity used in the current study (12 months) is an established threshold, but it is used less frequently than the 3- and 6-month thresholds. The rationale for employing the use of the 12-month threshold was that, in a clinical population familiar with persistent, debilitating conditions, the highest of the three established thresholds would be most appropriate. Had the lowest of the established thresholds (3 months) been used, the prevalence would not have altered substantially (58%), and would still have fallen within the range reported in the literature. The prevalence reported in the current study may, however, be an underestimate: whilst those that were excluded due to not having completed a BPI-SF were generally representative of the study cohort in terms of sociodemographic characteristics, an incomplete battery of tests suggests that patients were more unwell or 'chaotic' than those

that completed a full battery of tests, since they were likely to have missed more routine clinical appointments during the testing phase. Staff were instructed to complete all instruments with all patients, irrespective of whether or not they were experiencing relevant problems. For example, if an individual had no pain problems, staff were still required to administer a BPI-SF, indicating that there were no pain problems. There is, however, no guarantee of adherence to these instructions and staff may have failed to administer the BPI-SF to some patients without pain problems (Smith *et al.*, 2005), thereby, resulting in an overestimate of chronic pain.

7.1.2 Mortality in ORT patients with comorbid chronic pain within the context of the current literature

A substantial proportion of the overall cohort was deceased at follow-up; however, a significantly greater proportion of the comorbid pain group died during this period (11%) compared with the group with no pain (6%). The survivor bias (or 'survivor effect') should be borne in mind when interpreting the remainder of the findings, since the patients that died would have been likely to have had more problems and poorer health. The effect of the survivor bias, in this context, would be an underestimation of problems and an overestimation of wellbeing, particularly in the comorbid pain group. In consequence, there would be a muting of group differences in cases where the comorbid pain group was associated with poorer outcomes.

Higher proportions of the comorbid pain group had medical morbidities as the primary cause of death, whilst higher proportions of the group with no pain had experienced intentional self-harm (i.e. suicide), unintentional poisoning (i.e. overdose) and sequelae of substance use. The mean age at time of death in the comorbid pain group was 42 years, indicating severe medical morbidity at a relatively young age in this group. The primary causes of death in the group with no pain indicate 'chaotic', high-risk lifestyles and severe substance use problems. Indeed, unintentional poisoning was characterised in this group by a predominance of heroin, compared with a relatively equal mix of methadone, benzodiazepines and antidepressants in the comorbid pain group. Differentiating between suicide and accidental overdose is notoriously difficult to achieve and, given the drugs present in toxicology in the comorbid pain group, the identification of unintentional poisoning as the primary cause of death is perhaps questionable.

7.1.3 Illicit substance use in ORT patients with comorbid chronic pain within the context of the current literature

The significantly elevated prevalence of illicit use of any substances in patients with chronic pain (93%), compared with those with no pain (88%), is representative of other findings reported in the literature (e.g. Sharpe Potter *et al.*, 2008; Trafton *et al.*, 2004). The principal difference between the findings of this study and other reported studies is the substantially higher prevalence of illicit substance use in both groups in the current study; indeed, the majority of patients in both groups reported illicit use of substances. There may be a number of reasons for the disparity in the findings of this study compared with those other published findings. First, comparative studies were conducted in North America using government or privately insured clinical cohorts. In order to be retained in insurance-funded treatment, patients are usually required to demonstrate a positive response to that treatment. In ORT programmes, this is generally demonstrated by cessation of illicit use or, in the shorter-term, evidence of continually decreasing use. It is, therefore, not surprising that a comparatively higher prevalence of illicit use was found in the current study, which focused on an NHS-treated clinical population. Secondly, a variety of measures of treatment response were used across studies, thereby weakening the capacity for accurate comparison. Some studies used biochemical drug screening whilst some relied solely on patient reports of illicit substance use. Where continued treatment is dependent upon positive treatment responses, however, patient reports may be unreliable. Some studies used standardised questionnaire-based instruments; however, given the variation in ORT programme requirements of patients and, in consequence, patients' willingness to honestly disclose illicit substance use, validation of such instruments in a specific population may not be as translatable as many other types of standardised instrumentation in different fields of research. Thirdly, in comparison to the current study, many other studies assessed response to ORT treatment over relatively short time periods of up to 3 months (e.g. Rosenblum, 2003; Ilgen, 2006; Barry, 2009). Opioid dependence is known to be a chronic, relapsing condition with most patients receiving ORT treatment over a period of years rather than months (NIDA, 2012; Bart, 2012). As such, the value in assessing relatively short-term outcomes is questionable. In the current study, assessment was undertaken during a 5-year follow-up period, which may further explain the disparity in findings.

Contrary to the overall findings, a significantly higher proportion of the group with no pain reported illicit heroin use, and significantly more frequent use, at study inception. This finding was not corroborated by biochemical drug screen results. This may be a result of urinalysis not screening, specifically, for heroin; therefore, opioid screens also included illicit use of opioid analgesics, but not methadone. Since non-medical use of opioid analgesics did not differ by

group at study inception, however, it is unlikely to be the reason for non-corroboration of patent reported use. This finding may be more likely to be an artefact of the short half-life of heroin (~30 minutes for a single dose) and the time between drug use and testing, resulting in patient-reported heroin use but negative urinalysis findings. Heroin is the primary drug of misuse in most patients entering ORT programmes and, as such, is the principal drug of concern when assessing response to ORT treatment. Furthermore, clean opioid drug screens are often a requirement in ORT programmes for continued treatment delivery. This finding may reflect efforts in the comorbid pain group to conform to treatment agreements or it may reflect relative instability in patients with no pain. Illicit heroin use, specifically, was not assessed during the follow-up period but there was no group difference concerning illicit opioid use at 5-year follow-up. Survivor bias may have accounted for the absence of significant findings – i.e. it is the more unhealthy patients that are likely to have died during the observation period, and the elevated mortality in the comorbid pain group suggests that a relatively greater proportion of that group was not present at follow-up to report illicit drug use. Around a third of each group continued to misuse opioids; a slight reduction from around half of each group at study inception. Following at least 5 years of methadone maintenance therapy, however, this is still a substantial proportion of the cohort not yet stabilised in treatment.

Around a third of each group reported nonmedical use of diazepam at study inception; however, urinalysis indicated a substantially higher proportion of nonmedical benzodiazepine use in each group. Furthermore, urinalysis demonstrated that a significantly higher proportion of the comorbid pain group was engaged in nonmedical benzodiazepine use compared with ORT patients with no pain. The disparity between urinalysis and patient reports may reflect substantial use of benzodiazepines other than diazepam or may reflect efforts to conceal nonmedical use of benzodiazepines in both groups, but particularly in the comorbid pain group. Benzodiazepines are frequently used in conjunction with heroin or other opioids to intensify the euphoric experience; as such, benzodiazepine use may be viewed as part of the profile of 'problematic drug use' and patients may feel a need to conceal its use. This highlights the value in using objective measures of substance use to corroborate patient reports. Furthermore, since considerably more than half of each group was prescribed benzodiazepines during the follow-up period, patients may have been concerned about disclosing nonmedical use for fear of having their prescriptions reduced or stopped. Significantly elevated use in the comorbid pain group continued during the follow-up period, as shown by urinalysis. At 5-year follow-up, whilst the proportion of nonmedical benzodiazepine use in ORT patients with no pain had decreased, the proportion of use in the comorbid pain group had increased to almost three quarters of the group. Benzodiazepines are frequently used as an adjunct to analgesia or as a muscle relaxant

as part of a pain management regimen. The significantly elevated, and increasing, use over the follow-up period in the comorbid pain group may indicate pseudoaddiction in this group, whereby patients were attempting to alleviate unmanaged pain.

A substantial proportion of each group reported illicit cannabinoid use at study inception and these reports were corroborated by urinalysis. Cannabinoid use may be seen as less of a priority in ORT programmes, primarily because physical dependence on cannabinoids has not been demonstrated (Gordon *et al.*, 2013). In consequence, patients may be less concerned about disclosing illicit cannabinoid use, hence the corroboration of self-report by drug screen results. A significantly higher proportion of the comorbid pain group was engaged in illicit cannabinoid use compared with ORT patients with no pain at study inception, and this disparity continued during the follow-up period. The analgesic effect of cannabinoids has been well-demonstrated in both preclinical and clinical models and, furthermore, cannabinoids have been associated with an opioid sparing effect (Elikottil *et al.*, 2013). The significantly elevated use in the comorbid pain group may, therefore, indicate pseudoaddiction in patients whose pain is not well-managed or even untreated.

Sleep disorders develop commonly in patients with chronic pain (Menefee *et al.*, 2000). In the present study, sleep interference of pain was reported by more than three quarters of the comorbid pain group. In contrast to the present study, in which a binary sleep interference variable was computed, many studies have reported a mean sleep interference value for comorbid pain groups, using the BPI-SF, and reported findings of around 6-7 on a 0-10 scale (e.g. Dhingra et al., 2013; Jamison et al., 2009). In contrast, however, Rosenblum and colleagues (2003) used a score of 5 or higher on the BPI-SF scale as indicative of sleep interference, thereby creating a binary variable and, similar to the present study, reported that pain interfered with sleep in 73% of methadone-maintained patients with chronic pain. Despite the high prevalence of sleep interference in the present study, a relatively small proportion of the comorbid pain group was in receipt of prescribed medication for the treatment of insomnia at study inception (12%), and this did not vary by much during the follow-up period. This is similar to the finding of Jamison and colleagues (2000) who reported that 5% of methadone-maintained patients with chronic pain were in receipt of prescribed medication for the treatment of insomnia. Given the high prevalence of sleep disturbance and the substantially smaller proportion of the group in receipt of treatment for insomnia, efforts to manage sleep problems may account for some proportion of the illicit and nonmedical substance misuse in the comorbid pain group.

7.1.4 Group differences in ORT treatment and long-term illicit substance use associated with opioid treatment

Whilst the comorbid pain group was in receipt of a significantly higher mean methadone dose at study inception and a significantly higher proportion of this group was in receipt of prescribed benzodiazepines, the two principal medications prescribed by the service, they were significantly less satisfied with ORT treatment. This finding may be indicative of their pain problems – leading to physical distress, affective distress, poor wellbeing and poor functioning – rather than a comment on ORT treatment *per se*. Pain specialists and general psychiatrists are often reluctant to treat opioid-dependent patients, perhaps because the necessary precedents for collaborative working are not currently in place or because there are insufficient resources to facilitate this type of work. In consequence, opioid-dependent patients with comorbid pain and psychiatric disorders often must rely on ORT programmes for their treatment. Since managing pain syndromes and psychiatric distress is not of primary concern in ORT services, and the required expertise and resources are generally not available in these treatment settings, it is perhaps unsurprising that patients report treatment dissatisfaction.

Increasing opioid doses for ORT treatment were protective of continuation of illicit opioid use during the follow-up period in the comorbid pain group but not in the group with no pain. This means that increasing opioid dose was associated with cessation of illicit opioid use. This finding may be indicative of pseudoaddiction in the comorbid pain group, whereby eventual control of pain was associated with reduced illicit opioid use. Conversely, however, increasing total opioid dose (analgesic plus ORT opioids) was predictive of continuation of nonmedical benzodiazepine use and illicit cannabinoid use in the comorbid pain group but not in the group with no pain. These findings are difficult to interpret without an understanding of patients' motives for this substance misuse. The reduction of illicit opioid use but not of the other two substances may represent efforts to conform to ORT treatment requirements – whereby, opioids are seen as the 'target' drug – whilst still using illicit substances to enhance the euphoric effect of prescription opioids. Alternatively, it may indicate that this patient group continues to experience significant pain problems and that they are attempting to control their pain, whilst adhering to ORT treatment requirements concerning opioids, by using other drugs known to have analgesic properties. There is a need to understand how increasing opioid doses impact on pain. It may have proven ineffective in managing these patients' symptoms – indeed, such consistent and high doses could place patients at risk of developing opioid-induced hyperalgesia and, in consequence, exacerbate their pain problems. In this case, patients may have continued illicit use of some substances whilst adhering to the key treatment aim of reducing illicit opioid use. Indeed, there is evidence to suggest that opioid-induced hyperalgesia is dose-dependent

(Hooten *et al.*, 2010); therefore, the analgesic effects of benzodiazepines and cannabinoids may actually have proven more effective in managing pain, than the previously-used illicit opioids, alongside escalating prescription opioid doses.

7.1.5 Medical comorbidities associated with CP in ORT programme

A significantly higher proportion of the comorbid pain group reported physical health problems at study inception and this finding was corroborated by a significantly higher mean score on the MAP physical health subscale. This standardised subscale is problem-scored; therefore, a higher score is indicative of greater symptom severity. This may reflect the presence of chronic pain and is not necessarily indicative of additional medical morbidities. In an effort to identify specific problems with physical health, group differences on the individual subscale items were assessed; however, a significantly higher proportion of the comorbid pain group reported 'often' experiencing all signs and symptoms addressed by this subscale. Each of the subscale items, however, may reflect either physical health problems associated with the presence of chronic pain or side effects of treatment for chronic pain. Whilst these findings do not necessarily indicate medical morbidity beyond that of chronic pain, they do highlight the additional challenges in effectively treating these 'comorbid' patients within an ORT clinical setting.

Routinely-available, community-dispensed prescribing data were used to provide a proxy indicator of clinically significant medical morbidity in the cohort. BNF chapters and sections were used in the identification of prescribed medication indicative of severe and/or chronic disorders. In addition to analgesic treatment, a substantial proportion of the entire cohort was in receipt of prescribed medication for the treatment of chronic bowel disorders, cardiovascular disease, undernourishment and epilepsy. The first three are common comorbid conditions in opioid-dependent populations. The significantly elevated proportion of the comorbid pain group being in receipt of prescribed medication for the treatment of chronic bowel disorders may reflect the significantly higher methadone dose in this group, since opioid-induced constipation, and associated bowel disorders, are common problems in opioid-treated populations. This occurs via several mechanisms: stools are dried by increased water absorption from the small and large colon; increased sphincter tone; and decreased defaecation reflex. Many studies have shown that the severity of bowel dysfunction is associated with opioid dose and that this is reversed, in a dose-dependent manner, by opioid antagonists (e.g. Meissner *et al.*, 2009; Webster *et al.*, 2013); however, other studies have shown that formulation is more important than dose, *per se*. For example, fentanyl patches, even at high morphine-equivalent doses, have been shown to have a less constipating effect than oral opioids (Clark *et al.*, 2004); however, this finding is not consistently demonstrated in the literature (Weschules *et al.*, 2006).

Furthermore, almost a fifth of the comorbid pain group was in receipt of prescribed NSAIDs, another medication which is associated with gastric complications and contributes to bowel dysfunction (Klein et al., 2010). In addition, many patients with pain are likely to use OTC NSAIDs; however, since these medications are obtained OTC, it is not possible to construct a complete record of medicinal analgesic use in this study. It is of clinical importance to understand the characteristics of prescribed and OTC medication impacting on this common side effect so that it can be treated or managed in patients with chronic pain problems. Whilst often dismissed as a trivial side effect, chronic constipation has an adverse effect on patient quality of life, and can contribute significantly to increased morbidity and mortality by inducing haemorrhoid formation, rectal pain and burning, bowel obstruction and potential bowel rupture.

The high prescribing rate of anticonvulsant medication in the cohort is, on initial consideration, perhaps surprising. Furthermore, a significantly higher proportion of the comorbid pain group was in receipt of prescribed anticonvulsant medication at study inception compared with patients with no pain. Whilst the proportion of each group in receipt of anticonvulsant medication increased during the follow-up period, the relatively greater increase in the group with no pain resulted in no significant group difference at 5-year follow-up. Whilst the UK prevalence of epilepsy is estimated to be 0.97% and the Scottish prevalence slightly higher at 1.03% (Joint Epilepsy Council, 2011), 26% of the CP group and 15% of the NoP group were in receipt of anticonvulsant medication at study inception. Dennis and colleagues (2014) reported a prevalence of 2.13% of epilepsy in an opioid-dependent, methadone-maintained clinical population, which is substantially lower than the findings suggested by the amount of anticonvulsant prescribing identified in the present study. Since Dennis and colleagues relied on patient reports of comorbid epilepsy, rather than assessing prescribed anticonvulsant medication, this suggests that a substantial proportion of these prescriptions in the present cohort may have been intended to treat other disorders and, in ORT populations, which are known to have a high prevalence of psychiatric disorders, a proportion of this prescribing may have been intended to treat bipolar disorder. Furthermore, the significant group difference may indicate that a proportion of the comorbid pain group was in receipt of anticonvulsants for the treatment of neuropathic pain.

7.1.6 Psychiatric comorbidities associated with CP in ORT programme

Psychiatric illness is common in patients with chronic pain and in opioid-dependent patients, and the findings of the present study suggest that there may be a compounding effect in opioid-dependent patients with comorbid chronic pain. A significantly higher proportion of the

comorbid pain group reported mental health problems; however, a substantial proportion of the group with no pain also reported mental health problems. Interestingly, evidence of psychiatric 'caseness' using standardised instruments suggested that the prevalence of psychiatric problems was greater in both groups than was indicated by patient reports. The disparity was found particularly in the comorbid pain group, with more patients apparently underestimating the presence of psychiatric problems than in patients with no pain. Indeed, whilst 52% of the comorbid pain group reported psychiatric problems, 74% scored within the clinical range on the CORE. Patients with chronic pain tend to minimise their psychological distress, fearing that their pain symptoms may be dismissed as mental disorders (Cheatle *et al.*, 2006). This highlights the need for psychiatric assessments in clinical populations known to be at risk of psychiatric problems, rather than expecting patients to be aware of their treatment needs in the context of complex and debilitating clinical symptoms. The high prevalence of psychiatric morbidity, particularly in the comorbid pain group, is likely to have an adverse effect on quality of life in patients that already have a substantial health burden, and to render treatment ineffective where attempts are made to treat any of these conditions in isolation.

At study inception, the comorbid pain group was consistently associated with significantly elevated anxiety- and mood-related symptom severity, poorer overall wellbeing and life functioning, and elevated risk of harm. During the observation period, a significantly higher proportion of the group was in receipt of prescribed anxiolytics and anticonvulsants (a proportion of which were likely to have been used in the treatment of bipolar disorders, as discussed previously) but, despite elevated mood-related symptom severity, there was no significant group difference in treatment for depression. Elevated prevalence of depressive disorders in the comorbid pain group is consistent with the findings of other studies (Barry *et al.*, 2009; Trafton *et al.*, 2004; Dhingra *et al.*, 2013; Stevenson *et al.*, 2014; Morasco *et al.*, 2011). Jamison and colleagues (2000) reported medication use for specific psychiatric disorders in this comorbid population. They reported that antidepressant medication was prescribed to 28% of the comorbid pain group compared with 15% of methadone-maintained patients with no pain. This is substantially lower than the findings of the present study, where almost three quarters of both groups were prescribed antidepressant medication at any point during the observation period. The disparity in findings between the studies may reflect ease of access to treatment in these two populations. Jamison and colleagues undertook their study in a North American population and indicated that almost three quarters of their study cohort were in receipt of financial aid (and, presumably, eligible for Medicaid/Medicare), whereas, the present cohort had access to NHS treatment resources. Prior authorisation and financial reimbursement requirements associated with US governmental health insurance may mean that access to

specific treatments is limited compared with NHS treatment access. Furthermore, the present study assessed findings over a long-term follow-up period, compared with cross-sectional observations in the work undertaken by Jamison and colleagues. In each year of the observation period, however, around 40% of both groups were in receipt of antidepressant medication and there were no group differences at any time point during this period. The absence of group differences concerning treatment may reflect the unrecognised psychiatric distress which was noted particularly in the comorbid pain group and, again, highlights the importance of psychiatric assessment in clinical populations at risk of psychiatric illness. The relationship between depression, chronic pain and opioid dependence is dynamic, and effective treatment of any one is unlikely to be achieved in isolation from the others.

The elevated prevalence of treatment for possible bipolar disorder in the comorbid pain group may reflect the more 'chaotic' symptoms associated with this condition. As a note of caution in interpreting this finding, however, these medications may also be used in the treatment of neuropathic pain. Had the proportion of prescribing been close to zero in the group with no pain, it would have appeared likely that these medications were prescribed for the treatment of neuropathic pain in the comorbid pain group; however, prescribing in the group with no pain was also high (15% compared with 26% in the comorbid pain group). The prevalence of co-occurring opioid-dependence and bipolar disorder is high (Cerullo et al., 2007; Chengappa et al., 2000) and comorbid presentation is associated with increased substance misuse (Maremmani et al., 2012). Whilst it cannot be ascertained definitively, these findings suggest that a clinically-significant proportion of anticonvulsant medication may have been prescribed for the treatment of bipolar disorder. Irrespective of whether patients recognise psychiatric distress, the symptoms common in this disorder render it difficult to ignore. Furthermore, the family and friends of patients with bipolar disorder are more likely to highlight their concerns to physicians since the nature of this disorder necessarily impacts upon those around the patient, thereby negating some of the need for the patient to recognise their own psychiatric distress. There was a slight increase in prescribing in both groups during the follow-up period, but the increase was greater in the group with no pain, such that there was no group difference at follow-up. In consequence, this did not reflect effective treatment in the comorbid pain group but, rather, increased prevalence of potential treatment for bipolar disorder in the overall cohort. Bipolar disorder and chronic pain are common comorbidities. In a recent meta-analysis (Stubbs *et al.*, 2015), the prevalence of chronic pain in patients with bipolar disorder was shown to be 29%, and Birgenheir *et al.* (2013) reported that patients diagnosed with bipolar disorder report around four pain problems at any point in time. Furthermore, Hirschfeld and Vornik (2005) reported that 56% of patients diagnosed with bipolar disorder were dependent on substances.

Due to the nature of these conditions, bipolar disorder and opioid dependence are both associated with elevated risk of unstable states and physical injury and, consequently, persistent pain. Furthermore, substance dependence in patients with bipolar disorder is associated with a desire to manage the emotional and behavioural extremes that characterise this disorder. The dynamic relationship between these conditions necessitates the effective management of all three in successfully treating patients with this comorbidity cluster.

The significantly elevated presence of anxiety-related symptoms in the comorbid pain group is consistent with the findings of other studies (Barry *et al.*, 2009; Trafton *et al.*, 2004; Stevenson *et al.*, 2014; Morasco *et al.*, 2011). Studies generally reported either mean anxiety subscale scores, using different measures, or provided an amalgamated prevalence estimate of anxiety and depression. Trafton *et al.* (2004) reported anxiety in 59% of ORT patients with comorbid chronic pain, a substantially higher proportion than the 37% treated for anxiety at study inception in the present study. Trafton and colleagues conducted their study in a veteran population which may account for the relatively elevated proportion of anxiety found, due to the relatively high prevalence of posttraumatic stress disorder (PTSD) generally found in these populations (Gates *et al.*, 2012; Richardson *et al.*, 2011). Jamison and colleagues (2000) reported medication use for specific psychiatric disorders in this comorbid population. Sedative medication was prescribed to 47% of the comorbid pain group compared with 34% of methadone-maintained patients with no pain. This finding is also substantially higher than that of the 37% and 24%, respectively, found in the present study. Given the high prevalence of anxiety-related symptoms in the present cohort, and particularly in the comorbid pain group, this may indicate undertreatment in both groups and may be associated with the substantial nonmedical benzodiazepine use in both groups. The significantly elevated misuse in the comorbid pain group may indicate an effort to manage both psychiatric distress and pain problems, through the analgesic, muscle relaxant, effect of benzodiazepines. Despite comparatively less anxiolytic treatment in the present cohort, in addition to a significantly higher proportion of the comorbid pain group being in receipt of prescribed medication for the treatment of anxiety at study inception, this group was also associated with a significantly higher mean diazepam-equivalent dose during the follow-up period. Whilst undertreatment may be a problem, the comorbid pain group was clearly associated with more anxiety-related symptoms. Persistent and debilitating pain can exacerbate ongoing anxiety or can induce pain anxiety or pain catastrophisation (Kroenke *et al.*, 2013). This is a dynamic relationship which can, eventually, exacerbate both pain and anxiety in patients. There was, however, a reduction in the proportion of each group treated with anxiolytics during the follow-up period, but particularly in the comorbid pain group, and a mean dose reduction in those remaining on

treatment. These reductions may be driven by concern for patients; benzodiazepines are a commonly-used drug of abuse, particularly in opioid-dependent patients, since benzodiazepines are known to enhance the euphoric effect of opioids and may potentiate substance misuse (Jones *et al.*, 2012). Furthermore, cytochrome P450 assumes a role in the metabolism of opioids and in certain benzodiazepines, inhibitors of which can lead to decreased clearance of these drugs, thereby increasing risk of overdose and accidental death (Gudin *et al.*, 2013; Jones *et al.*, 2012).

7.2 Clinical implications associated with patient-attributed causal relationship between chronic pain and opioid dependence

As far as the author is aware, this work has not yet been examined in the literature. A similar piece of work was undertaken by Ilgen and colleagues (2010); however, rather than attempt to establish a causal relationship between chronic pain and opioid dependence, they examined the relative temporal onset of pain and substance use disorders. Furthermore, they included patients with a lifetime history of a substance use disorder, rather than current disorders, and patients with any substance use disorder, which included drug or alcohol dependence or abuse.

7.2.1 Identification of patient-attributed causal relationship between chronic pain and opioid dependence

In contrast to the findings of Ilgen and colleagues, the majority of the present cohort reported the belief that chronic pain had caused opioid dependence. Similar to the present study, they relied on patient reports regarding the relative temporal onset of these two disorders; however, since they were concerned with lifetime history of substance use disorders, patients' ability to recall accurately may have impacted more on their findings. Since the patients in the present study were currently in ORT, however, they may have been motivated to 'justify' their substance misuse by overstating the impact of pain. Perhaps the most relevant difference within this context, however, is that, whilst the present study focused solely on opioid dependence, Ilgen and colleagues included patients with any substance use disorder. Whilst there is an obvious link between exposure to opioids and opioid dependence or abuse, the inclusion in their cohort of patients who had had any substance use disorder may have resulted in a diluting effect. Familiarity with opioids and a drive to misuse them is perhaps more likely to be associated with subsequent opioid dependence or abuse rather than misuse of other drugs. In consequence, it is perhaps unsurprising that a substantially higher proportion of the present study, compared with the findings of Ilgen and colleagues, reported that pain preceded opioid dependence.

A high proportion (over two thirds) of the current cohort reported the belief that they became opioid-dependent as a consequence of pre-existing pain problems. This findings suggests that, perhaps contrary to expectation, a high proportion of patients in ORT programmes present for this treatment as a consequence of pain problems. There is no available information on the mechanisms responsible for the development of opioid dependence in this group but, presumably, a proportion will have developed iatrogenic dependence on opioids. Acute dependence following opioid exposure is common and considered to be normal; however, ongoing dependence or abuse is considered to be an aberration (Prater *et al.*, 2002). Additional factors may also impact on the development of opioid dependence or abuse. Patients may enter this state through attempts to control unmanaged pain (i.e. 'pseudoaddiction') or, recognising the euphoric effects of opioids, to control unmanaged psychiatric distress. Patients in ORT are associated with chronic, debilitating symptoms and poor recovery rates (Bart, 2012). Whilst there have been a number of studies examining sociodemographic and clinical predictors of aberrant drug use following exposure to opioid analgesics (e.g. Sehgal *et al.*, 2012; Cicero *et al.,* 2007; Fitzcharles *et al.,* 2011; Spiller *et al.,* 2009; Denisco *et al.*, 2012; Edlund *et al.,* 2010; Wasan *et al.,* 2007; Schieffer *et al.,* 2005), future studies should consider deriving predictive models of the development of clinically-diagnostic opioid dependence and, in particular, the development of severe disorders that require ORT for symptom management.

7.2.2 Sociodemographic characteristics associated with patient-attributed causal relationship between chronic pain and opioid dependence

The sociodemographic profile was similar in both groups; they were broadly characterised by a high proportion of males, a mean age of mid-30s, substantial socioeconomic deprivation, poor educational attainment, high unemployment and a substantial proportion of children living outside of the family home. This is a fairly typical sociodemographic profile for opioid-dependent patients in ORT (Sehgal *et al.*, 2012; Denisco *et al.*, 2012; Webster and Webster, 2005); however, what is surprising is the high proportion (more than two thirds) of males in the group reporting that chronic pain had caused opioid dependence. A number of studies have reported that females in receipt of opioid analgesic treatment are more likely to engage in aberrant drug-related behaviours – e.g. more likely to hoard unused medication, use additional medication to enhance the effectiveness of analgesics and use alternative routes of administration, such as crushing and snorting tablets (Back et al., 2009). Contrary to these findings, however, Edlund and colleagues (2014), in a study examining incidence of clinically-diagnostic opioid abuse and dependence in patients exposed to opioid analgesic treatment, reported that 63% of those that developed opioid use disorders were male. This finding is very

similar to the 70% found in the present study, suggesting that, whilst females may be more likely to be associated with aberrant drug-related behaviours, males may be more likely to develop clinically-diagnosed opioid use disorders. This further substantiates the suggestion that future studies should consider patients engaging in aberrant drug-related behaviours and patients with a diagnosis of opioid use disorders as distinct outcome groups and that further work is required to understand the sociodemographic and clinical factors impacting on the development of opioid dependence and abuse disorders in patients with chronic pain.

7.2.3 Illicit substance use, pain characteristics and stabilisation in ORT treatment associated with patient-attributed causal relationship between chronic pain and opioid dependence

Compared with the group reporting that chronic pain caused opioid dependence, a significantly higher proportion of the group reporting that dependence caused pain reported: illicit use; use of multiple substances; more intravenous drug use; and, generally, these patients were engaging in more frequent use of illicit substances. This 'chaotic' profile may indicate that many patients in this group had not yet gained control over their substance use. Indeed, a significantly smaller proportion of this group was reported to be stabilised in ORT treatment and a significantly higher proportion was associated with risk of harm due to drug use. Whilst a significantly higher proportion of this group reported illicit use of opioid analgesics, of those that misused opioid analgesics, patients reporting that chronic pain caused opioid dependence were misusing these drugs more frequently. Since analgesic effectiveness is associated with more frequent dosing than is obtained in ORT, more frequent misuse of opioid analgesics in this group may indicate pseudoaddiction – efforts to control unmanaged pain. Indeed, this group was significantly associated with a longer mean duration of pain and a higher mean intensity of pain.

7.2.4 Medical and psychiatric morbidity associated with patient-attributed causal relationship between chronic pain and opioid dependence

Patients in the group reporting that opioid dependence caused chronic pain were significantly associated with a higher physical health score, indicative of poorer physical health, a higher number of admissions to general hospitals and a higher mean number of nights spent in inpatient facilities. Given that there were no group differences concerning receipt of prescribed medication for the treatment of severe and/or chronic medical morbidity, self-reported poorer physical health and more inpatient treatment may be a reflection of the relatively more 'chaotic' profile of this group, including inability to stabilise in ORT treatment. Patients with substance use disorders are associated with elevated risk of physical injury (Voon *et al.*, 2015) and the

sequelae of substance use, including cardiac and respiratory problems, endocrine complications and risk of infection (Cushman, 1980), perhaps resulting in elevated medical morbidity in these populations.

Patients in the group reporting that opioid dependence caused chronic pain were also associated with significantly more psychiatric morbidity. This finding is contrary to that of Ilgen and colleagues, who found no group differences concerning lifetime mood and anxiety disorders. This may, again, be a function of their study having included participants with any substance use disorder, since higher rates of psychiatric problems are commonly a function of affective distress states associated with opioid withdrawal (Janiri *et al.*, 2005; Handelsman *et al.*, 1992). In the present study, psychiatric 'caseness' and social phobia were evident in a significantly higher proportion of the group reporting that opioid dependence caused chronic pain, and these patients generated significantly higher subscale scores for social dysfunction, somatic symptoms, anxiety/insomnia, problems/symptoms, life functioning (problem-scored) and risk/harm. Furthermore, they spent more nights in psychiatric inpatient facilities. Whilst patients with chronic pain have a higher prevalence of psychiatric disorders, particularly mood and anxiety disorders, than the general population (e.g. de Heer *et al.*, 2014; Woo, 2010), those who reported that chronic pain caused opioid dependence appear to suffer less psychiatric distress than those who reported that opioid dependence caused chronic pain. There were, however, no group differences concerning psychotropic prescribing and these findings may underpin the 'chaotic' profile described in relation to this group. Whilst the term, 'pseudoaddiction' is currently confined to the pain literature, these findings suggest that under-treatment for psychiatric distress may result in 'chaotic' lifestyles and behaviours and, in ORT clinical populations, this could manifest as uncontrollable substance use problems.

7.2.5 ORT and analgesic treatment associated with patient-attributed causal relationship between chronic pain and opioid dependence

The group reporting that chronic pain caused opioid dependence was in receipt of a significantly higher mean dose of opioid analgesics, but there was no group difference concerning satisfaction with treatment for pain problems. There was no significant group difference concerning mean methadone dose; however, the group reporting that opioid dependence caused chronic pain was significantly more dissatisfied with ORT treatment. Despite being on a significantly lower dose of opioid analgesics, it appears that this group perceives opioid dependence to be their primary problem and, in consequence, they perceive that further ORT treatment, rather than analgesic treatment, would help to attenuate their problems. It is unclear whether this perception is accurate, is a desire for elevated methadone doses in a group

that does not have control of their substance use problems, or is a need for greater management of a number of debilitating symptoms, particularly psychiatric disorders, in a group of patients that perhaps have difficulty in dissecting and understanding the complex nature of their distress.

7.2.6 Predictors of initiation and continuation of illicit substance use associated with patient-attributed causal relationship between chronic pain and opioid dependence

Increasing age was protective of continuation of nonmedical benzodiazepine use during the follow-up period in the group reporting that chronic pain caused opioid dependence. This may be a function of increasing acceptance of pain and an increasing ability to develop effective coping strategies in the management of pain. Poorer overall physical health was predictive of initiation of illicit opioid use in this group but perceptions that pain problems were being taken seriously by treating physicians was protective of initiation of both illicit opioid and cannabinoid use. This finding may be related to pseudoaddiction, whereby patients who do not feel that their pain problems are being taken seriously, and perhaps believe their pain to be under-treated, turn to illicit opioid use to control unmanaged pain. Pain interference was predictive of continuation of illicit cannabinoid use in the group reporting that opioid dependence caused chronic pain. This may reflect efforts to control unmanaged pain in a group that identifies substance use as the cause of their current problems and may attempt to manage pain without using illicit opioids – the principal drug of concern in ORT programmes.

Psychiatric 'caseness' was predictive of initiation of illicit opioid, benzodiazepine and cannabinoid use in the group reporting that chronic pain caused opioid dependence. Furthermore, a range of specific disorders and symptoms were predictive of initiation of illicit opioid and benzodiazepine use in this group. It is clear that, in addition to pain and physical health, psychiatric health has a substantial impact on initiation of substance use in this group. Whilst this group was associated with significantly less psychiatric morbidity, it is clear that, where present, psychiatric distress assumes an important role in deterring effective treatment of illicit substance use. Conversely, psychiatric 'caseness' was predictive of continuation of illicit opioid use in the group reporting that opioid dependence caused chronic pain. Rather than being associated with relapse to opioid use, this group continued to misuse opioids during the observation period. This finding suggests that this group of patients, that identify opioid dependence as the cause of their current problems, may also identify opioids as a remedy, perhaps because there are no obvious alternative solutions. Further research is required on multidisciplinary approaches to treatment in these groups, since an holistic approach to

symptoms may prove more fruitful. A necessary precursor, however, would be to identify and profile patient groups for whom standard treatment has not proven successful.

Increasing prescription opioid doses were associated with initiation of illicit opioid and cannabinoid use in the group reporting that chronic pain caused opioid dependence. The analgesic effects of opioids and cannabinoids are well-known and this increased illicit use may be the result of unsuccessful attempts to induce analgesia through prescribed medication. Increasing opioid doses (prescribed doses compounded by initiation of illicit use) may, however, result in the development of opioid-induced hyperalgesia (OIH). Effective management of OIH is achieved by cessation, reduction or rotation of opioids (SIGN, 2013); however, this may seem counter-intuitive to patients who may attempt to control their further exacerbated pain by increasing illicit drug use. This may also account for the initiation of illicit cannabinoid use in this group. Increasing prescription opioid doses were associated with initiation of cannabinoids and continuation of illicit cannabinoid and nonmedical benzodiazepine use in the group reporting that opioid dependence caused chronic pain. This profile of drug use is commonly associated with patients with psychiatric problems (Grattan *et al.*, 2012; Brunette *et al.*, 2003; Diehl *et al.*, 2010) and, given the significantly higher prevalence of psychiatric distress and 'chaotic' characteristics in this group, this may be an attempt to manage affective distress. These findings further suggest the value in assessing multidisciplinary approaches, including addiction and pain specialists and general psychiatrists. Future studies should consider prospective assessment of treatment outcomes as a function of multidisciplinary interventions.

7.3 Incidence of iatrogenic dependence on opioids following exposure to opioid analgesics

The pooled incidence estimate of 4.7% is similar to the 3.3% incidence reported by Fishbain and colleagues (2008). They undertook a 'structured evidence-based' review of the incidence of opioid abuse/addiction. They used a wider outcome definition (including addiction) than that of the current review; however, this finding shows that, irrespective of whether or not patients were associated with a clinical diagnosis of a dependence disorder, estimated incidence was similar.

The incidence reported by Noble and colleagues (2010) was considerably lower than the current finding; they reported signs of opioid addiction in 0.27% of pooled participants (and 0.14% in studies that did not refer to any previous history of substance misuse); however, due to the

inclusion solely of case series in this part of their review, they were unable to compute a statistical pooled estimate of effect size using meta-analytical techniques. Minozzi and colleagues (2013) undertook a qualitative synthesis of incidence of opioid dependence and reported an incidence range of 0 to 24% (with a median of 0.5%). They did not, however, compute a pooled estimate of effect sizes. Similarly, in a qualitative synthesis, Littlejohn and colleagues (2004) identified prevalence, as opposed to incidence, rates of up to 24% dependence and 41% abuse. Furthermore, in the studies included by Littlejohn and colleagues, it was not made clear how the authors of included studies defined the varied terms that they used (dependence, withdrawal, addiction and abuse) and which, if any, indicated a clinical diagnosis. Despite examination of a similar question, the findings of these three reviews are not comparable to the current review in terms of outcome measures and statistical techniques. The calculation of averages and total percentages cannot take account of within-study variance in pooling methods and, in consequence, will generate relatively unreliable event rates.

In the remaining review (Vowles *et al.*, 2015), some of the included studies provided a single rate of misuse or addiction whilst others reported a range. To ensure synthesis of the full complement of studies, the authors of this review calculated both a minimum and a maximum rate and, where a single value was reported in studies, this value was used to represent both the minimum and the maximum. Whilst the reported prevalence rates of addiction are similar to the summary effect reported in the current review (4.3% and 4.7%, respectively), the reported prevalence rates of misuse were dramatically higher (69.4% and 69.5%, respectively). One explanation may be that Vowles and colleagues defined 'misuse' as opioid use contrary to directions irrespective of the presence of harm or adverse effects. This definition could include a substantial proportion of people engaging in non-problematic substance use and patients seeking or obtaining effective pain relief. One additional potential reason for elevated rates may be that, similar to Littlejohn and colleagues, Vowles and colleagues examined prevalence (existing cases) – rather than incidence (new cases) – of non-medical or illicit substance use. This would necessarily result in higher rates, since this would include people whose substance misuse preceded analgesic prescribing. Additionally, from a translational perspective, whilst prevalence is highly clinically relevant in providing information about the extent of the problem and associated resource requirements, examination of prevalence, rather than incidence, cannot contribute effectively to informing prescribing policy from the perspective of risk of iatrogenic dependence or abuse following opioid analgesic exposure.

As the present review highlights, there is a dearth of prospective data examining *de novo* incidence of opioid misuse following analgesic prescribing. There are a number of validity issues

concerning the commonly-used retrospective study designs. First, patients are, presumably, more likely to seek treatment for pain problems much earlier in disease development compared with the stage at which they are likely to seek treatment in the development of substance use disorders. Secondly, many retrospective studies do not specify a period prior to a diagnosis of substance use disorder in which prescription opioids use was assessed and many studies examine any period prior to diagnosis and, in consequence, may be identifying lifetime exposures. Thirdly, many retrospective studies must rely, to some degree at least, on patient reports, either directly during data collection or via information contained in case notes. Patients may be relatively more likely to report pain or analgesia as a precursor to opioid dependence in an attempt to avoid the stigma associated with dependence disorders.

Sensitivity analyses indicated significantly lower incidences in studies that diagnosed dependence disorders in accordance with ICD-9 criteria as compared with DSM-IV criteria. It is generally accepted that ICD criteria are typically somewhat more stringent than respective DSM criteria in producing a clinical diagnosis of many mental and behavioural disorders (e.g. Adometto *et al.*, 2012; NICE, 2013); it is, therefore, not surprising that a significantly lower incidence is associated with ICD-9 diagnostic criteria. Subgroup analyses also indicated a significantly lower incidence associated with strong opioids and longer-term analgesic prescribing. If the development of opioid dependence disorders is less likely in patients prescribed strong opioids in the longer term, this may suggest a mediatory role of pseudoaddiction, whereby patients in receipt of inadequate analgesia (for example, weak opioids prescribed over short-term periods) exhibit addiction-like behaviour in an effort to achieve successful pain management.

Effective pain management and opioid analgesic prescribing are key health concerns and ineffective management of these issues will necessarily confer substantial individual and societal burdens. The 4.7% incidence identified in the current review is substantially lower than is often assumed in clinical settings, and rates were lower among those with longer-term prescribing (>3 months) and those receiving strong rather than weak opioids. This suggests a more modest direct effect of opioid analgesic prescribing, even in the longer term, than is generally perceived on the development of dependence or abuse. This finding suggests that, since a primary driver for the reluctance to prescribe opioids is concern over iatrogenic dependence and abuse, patients with pain problems may be being unnecessarily under-treated. However, it remains important to note, and aim to prevent, this serious adverse effect, no matter its prevalence. Robust scientific evidence must underpin efficacious policy and practice and, as such, there is a requirement for well-designed, rigorously-controlled, adequately-powered, prospective

experimental studies examining the incidence – rather than prevalence – of iatrogenic opioid dependence and abuse following analgesic prescribing. Consideration should be given to the commissioning of a prospective registry with robust follow-up which would enable careful oversight of incidence to facilitate the development of preventative strategies. Furthermore, funders and commissioners should consider the potential for future meta-analyses when reviewing the study design, terminology definitions, outcome measures and statistical power of proposed future studies.

7.4 Evidence for the development of opioid-induced hyperalgesia in clinical populations

The findings of the current meta-analysis suggest that OIH may play a role in the lack of long-term effectiveness of opioid analgesics. OIH is characterised by aggravated pain compared with pain prior to opioid use or with the *de novo* development of pain in the absence of pathology. In consequence, it may also contribute to the high prevalence of chronic pain reported in patients in receipt of ORT for the treatment of opioid dependence, whereby chronic opioid administration contributes to the development of pain in these patients.

Elevated pain sensitivity was not observed in patients across all pain modalities. Whilst the evidence was fairly consistent across thermal (hot and cold) experimental pain models assessed by pain tolerance, elevated pain sensitivity was not observed in patients in response to noxious electrical stimulation. All but one of the studies that assessed responses to electrical stimuli also assessed responses to the cold-pressor test in the same samples. In contrast to the findings of electrical testing, a meta-analysis of the findings of these cold-pressor tests revealed significantly elevated pain sensitivity in patients compared with controls. It is not clear why responses to noxious electrical stimulation differed consistently to responses to noxious cold stimulation; however, there could be several potential reasons for this disparity. The obvious difference between thermal and electrical modalities is that the short bursts of electrical stimulation are likely to elicit phasic pain whilst the relatively longer-term exposure in thermal pain models is likely to elicit tonic pain, each associated with different pain qualities (Chen et al., 1985). Furthermore, it is proposed that tonic pain models more closely resemble clinical pain and that they are associated with different neurophysiological pathways and pharmacological modes of action than phasic pain models (Chen et al., 1989). This may explain, at least to some degree, the disparity between the consistent findings of thermal pain models and the findings of electrical pain models.

Pain has crucial adaptive functions in daily life which serve as a warning mechanism in the presence of harmful stimuli. The role of pain is of clear value in the presence of thermal or mechanical stimulation, which are relatively common in daily life, but its value in response to electrical stimulation is less obvious. Indeed, air is a poor conductor of electricity and, in consequence, humans have not developed electroreception; electroreceptors are generally present only in aquatic and amphibious animals since salt water is an effective medium for the conduction of electrical stimuli. It may be that, in evolutionary terms, central and peripheral nociceptive responses to thermal stimuli are 'hardwired' in human physiology but that responses to relatively uncommon stimuli, such as electricity, function differently. Further comparison of nociceptive responses in different experimental pain modalities is required to ensure the validity of assessment methods.

Whilst evaluation of the psychometric properties of QST techniques using electrical experimental pain models has been encouraging, there is considerably less evidence compared with thermally-induced pain. Furthermore, in the assessment of OIH, since there are no objective, clinically-observable effects of central sensitisation, face validity only has been examined and construct validity has not yet been established. Whilst the face validity and reliability of thermally-induced pain have been well-examined, further assessment of other experimental pain modalities is required. In the meantime, future research studies should consider using a battery of tests conducted in different experimental pain modalities to verify findings. QST techniques are not generally used in routine clinical practice but, following robust validation of these methods, they could prove valuable in helping to distinguish between opioid tolerance and OIH. In clinical assessment of pain it is difficult to distinguish between elevated pain sensitivity and decreased analgesic efficacy. In comparison with pain rating scales, however, QST enables pain assessment at non-painful sites – which could be more accurately compared with normal thresholds – thereby facilitating identification of pathology beyond that of tissue damage at painful sites (i.e. hyperalgesia).

Whilst it is generally assumed that the presence of OIH impacts on both pain threshold (i.e. detection of pain) and pain tolerance, the findings of this review suggest detection thresholds are similar in patients and controls and that significant group differences are associated only with pain tolerance. These findings are difficult to interpret without further empirical examination; however, they may reflect the findings of Harris and Rollman (1983). Using the Campbell and Fiske (1959) multitrait-multimethod matrix, they established a correlation matrix using pain modalities (i.e. multitrait) and measures of pain threshold and pain tolerance (i.e. multimethod) to evaluate convergent and discriminant validity. They concluded that pain

threshold and pain tolerance indicate different components of the pain experience, since correlations were higher for threshold (and for tolerance) across pain modalities than they were for threshold and tolerance within each modality. Furthermore, it is not possible to objectively distinguish the sensory and affective components of the pain experience. It has been proposed that pain detection threshold is simply a sensory threshold but that pain tolerance, which necessitates a behavioural response, is a function of both sensory and affective processing (Osterweis *et al.*, 1987). This may explain why there is little variation between patients' detection response times and why evidence of OIH is found only in assessment of pain tolerance. In light of the evidenced disparity in threshold and tolerance judgements, it is important that future studies assess both indices in the evaluation of responses to experimental pain. Furthermore, many patients experiencing chronic refractory pain are known to experience pain anxiety and to exhibit pain-related protective behaviours (Vlaeyen et al., 2000) and this may explain, to some degree, the relatively shorter time or smaller stimulus increment between pain detection threshold and pain tolerance. This potential confounder requires to be controlled in future studies, perhaps by standardised assessment of pain anxiety and catastrophisation.

Hyperalgesic states were more evident in opioid-dependent treatment groups than in patients with chronic pain. Compared with many other clinical populations, opioid-dependent patients are associated with greater life stress (Preston et al., 2011) and with increased prevalence of chronic illness, multimorbidity and attendance at emergency departments (O'Toole et al., 2014). It is, therefore, important that health assessments of these populations control for a range of factors, including affective characteristics and coping styles, which may impact on judgements of the pain experience. Patients in receipt of ORT are likely to be in receipt of considerably higher equivalent opioid doses than patients with chronic pain and this significant group difference may substantiate the dose-dependent relationship between opioids and hyperalgesia reported in a number of studies (e.g. Ackerman, 2006; Axelrod et al., 2007; Chung et al., 2004; Mercadante et al., 2005). The present review, however, found that elevated opioid doses were significantly associated with lower pain sensitivity. This finding requires further replication but may suggest that, in a proportion of patients at least, suspected hyperalgesia actually reflects inadequate analgesic treatment. The hypothesised decreased pain sensitivity associated with NMDA receptor antagonist treatments was not evidenced. Very few patient groups with chronic pain were in receipt of opioids with NMDA receptor antagonist properties – most were methadone-maintained patients treated for opioid dependence. This may be related to evidence suggesting that methadone has low NMDA receptor affinity (Callahan, 2004) or to continued illicit opioid use in patients. This suggestion is corroborated by the findings of Compton et al. (2001) when, only on controlling for illicit use, did they find a significant

differential effect between methadone and buprenorphine (albeit in the opposite direction). Further empirical examination of the role of NMDA receptor antagonism is required; this may involve the use of opioids with NMDA receptor antagonism properties –such as methadone or ketamine – in patients with chronic pain, the use of adjunctive NMDA antagonists or rigorous control of substance misuse in study participants.

The present review provides evidence of the development of opioid-induced hyperalgesia in humans but that this is dependent upon the nature of the noxious stimulus (e.g. thermal versus electrical stimulation) and whether pain detection threshold or pain tolerance was used in the assessment procedure. Patients in receipt of chronic opioid therapy were shown to be hyperalgesic to noxious thermal (hot and cold) stimuli assessed by pain tolerance. Hyperalgesic states were more evident in opioid-dependent patients and in treatment populations receiving opioids with NMDA receptor antagonist properties, but this primarily involved methadone-maintained opioid-dependent patients. Further studies must include evaluation of both pain threshold and pain tolerance across several pain modalities and must ensure more rigorous control of relevant characteristics within treatment groups, such as substance misuse, affective components or coping styles, and may consider using adjunctive NMDA receptor antagonists in attempting to identify effective treatment strategies whilst reducing the potential impact of opioid-induced hyperalgesia.

7.5 Limitations

7.5.1 Primary data analyses

There were several important limitations associated with the primary data analyses. First, study inception did not represent any form of baseline. At study inception, participants had been engaged with treatment services for varying lengths of time. Whilst the follow-up period permitted assessment of changes over time in outcome measures, not having been able to collect data from entry to treatment, or to control for length of time in treatment at study inception, resulted in a potential confounding variable.

Secondly, the study aimed to examine the entire treatment population in Tayside; however, data were not available for all patients in treatment. Data were collected by addiction specialist nurses at routine clinical appointments; therefore, patients for whom there were no data were likely to be patients that missed their routine appointments and may have been associated with more 'chaotic' profiles, more illicit substance use and poorer general health.

Thirdly, as a result of NHS service requirements, a modified version of the standardised Brief Pain Inventory – Short Form (BPI-SF) was used in the current study. Since a number of questions from the standardised instrument were omitted, it was not possible to compute the two BPI-SF domains, pain severity and pain interference. Furthermore, the conventionally-used 0-10 scale for reporting pain intensity was replaced by a 0-100 scale making it unwise to compare the findings of pain intensity with those of other studies. It cannot be assumed, for example, that the difference between 60 and 70 – or, indeed, 64 and 65 – on a 0-100 scale is perceived as the same as the difference between 6 and 7 on a 0-10 scale.

Fourthly, the mean dose of medication was computed in person-years: the mean dose was calculated for each patient for each year, and the mean average of the individuals' mean values was reported. Whilst it is acknowledged that prescription doses will have varied for individuals within each year of the observation period, mean dose was reported for each year of the observation period, rather than for each month within that period, since it would be difficult for the reader to make meaningful visual group comparisons of 72 data points. The limitation is the diluting effect of months during which individuals received no prescriptions and, in consequence, the mean values reported may be an underestimate of actual mean group dose in any given year. This method was, however, applied consistently during data coding processes; therefore, any group effects are unlikely to be a function of this process decision. Furthermore, significant group effects are actually likely to be an underestimate of the disparity between groups due to this diluting effect.

Fifthly, the number of prescriptions for each medication was also calculated in person-years: the number of prescriptions for each patient in each year was used to compute group mean values for each year. To facilitate inclusion of a meaningful number of participants in repeated-measures analyses, those that had been in receipt of particular medications at any point during the observation period were included, rather than only the very small number of participants that received medications consistently throughout the observation period. This resulted in the inclusion of participants that had received no prescriptions during some years, and these events were coded as zero. In consequence, there was a diluting effect similar to that described in relation to the calculation of mean doses. As a result, the values reported for number of prescriptions in each year are underestimates; however, since this method was applied consistently, any group effects could be considered valid. Indeed, significant group effects are actually likely to be an underestimate of the disparity between groups due to this diluting effect.

Finally, the patient-attributed causal relationship between opioid dependence and chronic pain relied upon patient accurate patient recall, understanding of the potential interactions of these two clinically complex conditions and patient candour. Using this approach was considered to be more valid and more meaningful than the available alternative, the temporal relationship between presentation for treatment of these two conditions, since patients are likely to perceive pain as problematic at onset but may perceive substance use as problematic at a comparatively later stage in disease development. It should be borne in mind, however, when interpreting the data, that some patients may have identified pain as the original primary disorder in an attempt to 'justify' illicit substance use.

7.5.2 Secondary data analyses

The obvious limitation of the secondary data analyses was that, due to pragmatic considerations, included articles were restricted to those written in English. Although beyond the author's control, as a result of the relatively small number of studies included, and the established observations to predictors ratio of 10:1, it was not possible to enter more than one explanatory variable into each meta-regression model and, therefore, it was not possible to derive complete models explaining heterogeneity.

7.6 Conclusions

Successful treatment in ORT programmes is not defined solely by abstinence from illicit drug use, but also general health and life functioning. Successful treatment is frequently compromised by comorbid pain and other medical and psychiatric comorbidities. The findings of the present study indicate that opioid-dependent patients with comorbid pain present with more complex and enduring clinical profiles, in addition to their pain problems, compared with opioid-dependent patients with no pain. In consequence, these 'comorbid' patients are associated with a range of additional treatment needs, including special pain treatment and general psychiatric interventions. The relationship between pain and affect is dynamic (Wilson-Poe *et al.*, 2017). Whilst the experience of persistent and debilitating pain can impact adversely on affective states, leading to depression and anxiety (Trivedi, 2004), stress and anxiety increase both muscle contraction and sympathetic outflow, which can initiate pain or exacerbate pre-existing pain (Burton *et al.*, 2016). Furthermore, the cognitive and affective components of depression can contribute to poor coping mechanisms, which, in turn, can increase anxiety and exacerbate ongoing pain problems (Woo, 2010). Whilst general psychiatrists are often reluctant to treat opioid-dependent patients, ORT programmes frequently do not have staff with

appropriate specialist training or the resources required to meet the needs of patients with chronic and debilitating general psychiatric disorders.

Similarly, the relationship between pain and opioid dependence is dynamic, and a number of factors need to be considered when attempting to address these comorbid conditions. First, whilst incidence of iatrogenic addiction to opioids following analgesic exposure appears to be low, analgesic treatment involving opioids, in patients with pre-existing opioid dependence, may further complicate ORT treatment. Secondly, poorly-managed pain problems may lead to pseudoaddiction. Patients' attempts to control unmanaged pain by misusing substances are unlikely to be successful and, furthermore, these behaviours are likely to compromise attempts to achieve abstinence from illicit substance use or stabilisation in ORT programmes. Successful treatment of these issues would necessarily require multidisciplinary approaches between pain and addiction specialists – not simply patient attendance at both services but also a collaborative approach between these specialist services. Thirdly, exposure to opioids can result in the development of opioid-induced hyperalgesia, further complicating pain management and ORT treatment in these patients. Whilst the appropriate response for effective pain management in hyperalgesic states brought about by opioid exposure is cessation, reduction or rotation of opioids, this is often not achievable in patients who require ORT to manage withdrawal symptoms. Many ORT programmes rely solely on methadone prescribing, although buprenorphine is becoming increasingly-available for patients stabilised on relatively low morphine-equivalent doses; however, this restricts the treatment options available to pain specialists involved in the management of these patients. Exploratory work has been undertaken on the potential role of a number of drugs, including NMDA receptor antagonists, in preventing the development of opioid-induced hyperalgesia or attenuating hyperalgesic symptoms (e.g. Mao *et al.* 2002 King *et al.*, 2005; Ossipov *et al.*, 2005; Mao, 2006). Future studies should examine the incidence of opioid-induced hyperalgesia, rather than simply demonstrating its development in clinical populations, to establish the extent of this problem, and further studies are required to assess the effectiveness of adjunctive medications with a potential to attenuate symptoms.

It is likely that a proportion of patients in receipt of ORT with comorbid chronic pain will have developed acute iatrogenic dependence on opioids following analgesic exposure, which may then develop into clinically-diagnostic chronic dependence or abuse. Furthermore, a proportion of patients with these comorbid conditions may have developed unmanageable, problematic opioid use as a function of having misused prescription analgesics or other opioids in an attempt to control unmanaged pain problems. Patients presenting with these comorbid conditions may,

however, develop these conditions in the opposite direction. Opioid-dependent patients are associated with substantially more medical morbidities than the general population, poorer self-care and increased risk of physical injury due to elevated risk-taking behaviours and 'chaotic' lifestyles. The development of pain problems in opioid-dependent patients is, therefore, more likely compared with the general population. Furthermore, chronic exposure to opioids, through illicit use and/or opioid replacement therapy, and the subsequent potential for the development of opioid-induced hyperalgesia, may exacerbate pain in opioid-dependent patients or result in the development of pain. Patients with chronic pain and opioid-dependent patients have some clinical similarities, such as higher prevalence of medical and psychiatric morbidities; however, where a causal relationship exists between the two in comorbid patients, effective treatment is dependent upon understanding whether the direction of that causal relationship is important. Future studies are required to further examine whether or not the causal direction results in two or more clinically-distinct treatment populations, and to profile the treatment requirements of these patient groups. In addressing these issues, it is important to consider motivation for illicit substance use, particularly in patients with comorbid chronic pain, to establish if it is driven by the euphoric effects of substances or associated with a desire to manage pain or the elevated psychiatric distressed observed in these patient groups.

In conclusion, the findings of the present study suggest that elevated medical and psychiatric morbidity is associated with chronic pain in opioid-dependent clinical populations, and that, within this comorbid group, there are subgroups that are associated with clinically-distinct profiles and treatment requirements. In consequence, there is a need for multidisciplinary clinical assessment and treatment, which must include pain and addiction specialist services and general psychiatric services. The multidisciplinary approach must ensure that it goes beyond simply encouraging patient attendance at multiple services; cohesive treatment plans must be developed through services communicating and contributing their expertise to the development of these plans. Future studies must focus on a number of key areas in contributing to the development of effective treatment strategies for the management of these clinically-complex conditions which interact dynamically, prevent recovery and perpetuate poor health.

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Appendix I: Quality assessment tool for observational cohort and cross-sectional studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			

12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Quality Rating (Good, Fair, or Poor) (see guidance)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for assessing the quality of observational cohort and cross-sectional studies can be found at: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort

Appendix II: Quality assessment tool for before-after (pre-post) studies with no control group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?			
2. Were eligibility/selection criteria for the study population prespecified and clearly described?			
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			
4. Were all eligible participants that met the prespecified entry criteria enrolled?			
5. Was the sample size sufficiently large to provide confidence in the findings?			
6. Was the test/service/intervention clearly described and delivered consistently across the study population?			
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?			
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?			
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?			
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?			
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the			

statistical analysis take into account the use of individual-level data to determine effects at the group level?			

Quality Rating (Good, Fair, or Poor) (see guidance)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for assessing the quality of before-after (pre-post) studies with no control group can be found at: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after

Appendix III: PROSPERO registration

(Incidence of iatrogenic opioid dependence or abuse in patients exposed to opioid analgesic treatment: A systematic review and meta-analysis)

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

Systematic review

Please complete all mandatory fields below (marked with an asterisk *) and as many of the non-mandatory fields as you can then click *Submit* to submit your registration. You don't need to complete everything in one go, this record will appear in your *My PROSPERO* section of the web site and you can continue to edit it until you are ready to submit. Click *Show help* below or click on the icon to see guidance on completing each section.

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Incidence of iatrogenic dependence on opioids in humans following chronic opioid analgesic exposure: systematic review and meta-analysis

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

16/01/2017

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/12/2017

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided. Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified. This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Cassie Higgins

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Cassie

7. * Named contact email.

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University of Dundee
Mailbox 6
Level 6
Laboratories Block
Ninewells Hospital Dundee
DD1 9SY

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.
+44 (0)1382 383619

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
University of Dundee

Organisation web address:

https://www.dundee.ac.uk/

11. Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Ms Cassie Higgins. University of Dundee

Professor Blair Smith. University of Dundee

Professor Keith Matthews. University of Dundee

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

None

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

What is the pooled incidence estimate of iatrogenic dependence on opioids in humans treated with chronic opioid analgesic therapy (COAT)?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

Electronic sources to be searched: PubMed; MEDLINE; CINAHL Plus; Embase; Web of Science; and OpenGrey.

The following search restrictions will be applied:

Language of publication: English.

Participants: Human.

Dates: Up to 01/04/17.

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Iatrogenic dependence on opioids following chronic opioid analgesic exposure.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Inclusions: Humans. Exclusions: Animals.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.
Exposure to chronic opioid analgesic treatment (COAT). 'Chronic exposure' is defined as prescribed on a daily (or near daily) basis for 7 days or more.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.
Not applicable.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.
Included: Randomised studies; experimental studies; clinical trials; observational studies; case controlled studies; cohort studies; and cross-sectional studies.
Excluded: secondary data analysis.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
This review aims to focus on a clinical diagnosis of opioid dependence or abuse (assessed in accordance with DSM or ICD criteria) rather than on addiction in its wider sense (indicated by aberrant drug-related behaviour (ADRB) such as drug-seeking behaviour in medical treatment settings). Included studies will have used clinical assessments or standardised instruments to demonstrate dependence/abuse. Studies will be excluded if they rely on patient reports or proxy indicators of dependence since it will be impossible to distinguish between dependence/abuse and addiction using these methods of data collection.

24. * Primary outcome(s).

Give the pre-specified primary (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.
Numbers/proportions of participants developing iatrogenic dependence on opioids.

25. * Secondary outcome(s).

List the pre-specified secondary (additional) outcomes of the review, with a similar level of detail to that required for primary outcomes. Where there are no secondary outcomes please state 'None' or 'Not applicable' as appropriate to the review
None.

26. Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Studies will be selected in accordance with the eligibility criteria outlined above. Titles and abstracts of search hits will be reviewed and irrelevant studies will be excluded. Articles retained at this stage will undergo full text review with further studies being excluded. A random selection of 10% of included articles will be reviewed by a review team member not involved in database searches or article selection. To avoid bias, the reviewer will be blind to author, journal and date of publication. Discrepancies will be discussed between the researcher and the reviewer and, where discrepancies remain, they will be addressed at review team meetings. Where discrepancies are not resolved at team meetings, studies will be included.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Risk of bias (RoB) assessment will be undertaken using the Scottish Intercollegiate Guidelines Network (SIGN) checklists (Harbour et al., 2001) and the Newcastle-Ottowa Scale (NOS) (Wells et al., 2000). There are specifically-tailored SIGN checklists for randomised, case-control and cohort study designs. The NOS was developed and refined using the Delphi process and is recommended by the Cochrane Collaboration. It provides specifically-tailored scales for both case-control and cohort study designs. Both assessments will be undertaken to maximise robustness of findings. The SIGN checklists will be used since they provide tailored assessments for randomised as well as case-control and cohort studies. The NOS will be used to generate a numerical score which will be used in sensitivity analyses.

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

Assuming the identification of sufficient homogenous studies, meta-analysis will generate a pooled estimate of the proportion of patients developing opioid dependence/abuse following COAT. Studies will be weighted using the principle of inverse-variance to avoid bias based on sample size. Heterogeneity will be assessed using the Chi-squared and I-squared statistics and an I-squared value of 50% will be considered to be evidence of substantial heterogeneity. A random effects model will be employed in light of anticipated heterogeneity. Sensitivity analyses will be undertaken based on study quality to test the generalisability of overall findings.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co- morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

Assuming the emergence of sufficiently-homogenous subsets of studies, several sub-groups (detailed below) will undergo additional meta-analysis.

1. Clinical diagnosis; dependence; abuse.
2. Demographic characteristics: gender; age; and ethnicity.
3. Socioeconomic characteristics: socioeconomic deprivation; and employment status.
4. Medical history: physical injury; substance use disorders; and other psychiatric disorders.
5. Clinical characteristics: chronic medical morbidities; psychiatric disorders (substance use disorder, depressive disorders, anxiety disorders and somatoform disorders); and nociceptive or neuropathic pain.
6. Treatment characteristics: strong or weak prescribed opioids; short- and long-acting opioids; and low or high analgesic opioid dose.
7. Personality traits: Neuroticism; extraversion; and conscientiousness.
8. Genetic risk for opioid dependence: OPRM1; OPRD1; O{RK1; DRD2; PDYN; CPY2B5; ABCB1 (MRD1); MYOCD; unigene cluster Hs. 147755; and intergenic variants.

Appendix IV: PROSPERO registration

(Evidence of opioid-induced hyperalgesia in clinical populations: A systematic review and meta-analysis)

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

Systematic review

Please complete all mandatory fields below (marked with an asterisk *) and as many of the non-mandatory fields as you can then click *Submit* to submit your registration. You don't need to complete everything in one go, this record will appear in your *My PROSPERO* section of the web site and you can continue to edit it until you are ready to submit. Click *Show help* below or click on the icon to see guidance on completing each section.

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Evidence for the development of opioid-induced hyperalgesia in humans: a systematic review and meta- analysis

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

01/02/2017

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/12/2017

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided. Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified. This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Cassie Higgins

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:
Cassie

7. * Named contact email.

Give the electronic mail address of the named contact.
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8. Named contact address

Give the full postal address for the named contact.
Division of Neuroscience
University of Dundee
Mailbox 6
Level 6
Laboratories Block
Ninewells Hospital Dundee
DD1 9SY

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.
+44 (0)1382-383619

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
University of Dundee

Organisation web address:
https://www.dundee.ac.uk/

11. * Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Ms Cassie Higgins, University of Dundee.
Professor Blair H Smith, University of Dundee.
Professor Keith Matthews, University of Dundee.

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.
None

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.
Opioid-dependent people maintained on opioid replacement therapy will have decreased PTR and/or PTO;
Formerly opioid-dependent people detoxified from opioids will have increased PTR and/or PTO;
People with chronic non-malignant pain who initiate long-term opioid analgesic therapy will develop decreased PTR and/or PTO;
People with chronic non-malignant pain who are decreasing, detoxifying or being withdrawn from opioid analgesic treatment will have increased PTR and/or PTO;
Opioid exposure in non-clinical populations will decrease PTR and/or PTO.

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
PubMed; MEDLINE; CINAHL Plus; Embase; Web of Science; ERIC; and OpenGrey will be searched Limitations: Human studies only.

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).
Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Opioid-induced hyperalgesia in humans

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusions: Included studies will focus exclusively on human populations [RQ1 Opioid-dependant people maintained on opioid replacement therapy; RQ2 Formerly opioid-dependant people detoxified from opioids; RQ3 People with chronic non-malignant pain who initiate long-term opioid analgesic therapy; RQ4 People with chronic non-malignant pain who are decreasing, detoxifying or being withdrawn from opioid analgesic treatment; and RQ5 Opioid exposure in non-clinical populations]

Exclusions: Animal models and studies focusing on malignancy-related pain

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Inclusions: Exposure to pain, irrespective of modality (e.g. mechanical, thermal, chemical, etc.)

Exclusions: No exposure to pain stimulus

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Inclusions: Comparator cohorts may include non-clinical or clinical controls who are not exposed to the same treatment as the target cohorts

Exclusions: No comparator cohort

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Inclusions: Randomised studies; experimental studies; clinical trials observational studies; case controlled studies; cohort studies; cross-sectional studies; and time series studies.

Exclusions: Case series; case reports; and secondary research

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

The intervention will be exposure to pain irrespective of modality (e.g. mechanical, thermal, chemical, etc.). Measures will focus on pain threshold (PTR) and pain tolerance (PTO). PTR is defined by time taken to report pain on exposure to a stimulus and PTO reflects time taken to withdrawal. If matched designs are employed, participants will be matched on, at least, age and gender. If significant socio-demographic differences are identified, these confounders should be controlled for in subsequent analyses.

24. * Primary outcome(s).

Give the pre-specified primary (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

First primary outcome: Mean difference in pain threshold (PTR). Second primary outcome: Mean difference in pain tolerance (PTO).

25. * Secondary outcome(s).

List the pre-specified secondary (additional) outcomes of the review, with a similar level of detail to that required for primary outcomes. Where there are no secondary outcomes please state 'None' or 'Not applicable' as appropriate to the review

None

26. Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Studies will be selected in accordance with the eligibility criteria outlined above. Titles and abstracts of search hits will be reviewed and irrelevant studies will be excluded. Articles retained at this stage will undergo full text review with further studies being excluded. Twenty percent of included articles will be reviewed by a review team member not involved in database searches or article selection. To avoid bias, the reviewer will be blind to author, journal and date of publication. Discrepancies will be discussed between the researcher and the reviewer and, where discrepancies remain, they will be addressed at review team meetings. Where discrepancies are not resolved, studies will be included.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Risk of bias (RoB) assessment will be undertaken using the CASP Randomised Controlled Trial Checklist (RCTC), the CASP Case Control Checklist (CCC) and the CASP Cohort Study Checklist (CSC).

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

Since all measures of PTR and PTO will necessarily consist in measures of time, meta-analysis will generate a pooled estimate of mean difference in time between groups for each of the research questions. Studies will be weighted using the principle of inverse-variance to avoid bias based on sample size. Heterogeneity will be assessed using the Chi-squared and I-squared statistics and an I-squared value of 50% will be considered to be evidence of substantial heterogeneity. A random effects model will be employed in light of anticipated heterogeneity. Sensitivity analyses will be undertaken based on study quality to test the generalisability of overall findings.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co- morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

Assuming the emergence of sufficiently-homogenous subsets of studies, three sub-groups will undergo additional meta-analysis:

1. Modality of pain exposure
2. Studies that controlled for opioid tolerance
3. Studies reporting treatment with an NMDAR antagonist (such as methadone or ketamine) versus opioids that are not active at NMDA receptor sites

Appendix V: List of publications and presentations

Publications

Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: A systematic review and meta-analysis. Accepted for publication pending minor amendments. British Journal of Anaesthesia.

Evidence of opioid-induced hyperalgesia in clinical populations following chronic opioid exposure: A systematic review and meta-analysis. In manuscript.

Presentations

Prevalence, experience and impact of chronic pain in an opioid dependent population. Oral presentation. Department of Psychiatry Seminar Series, University of Dundee (2012).

Psychiatric morbidity in opioid-dependent patients with comorbid chronic pain. Oral presentation. School of Medicine Postgraduate Research Student Symposium (2012).

Problematic substance use in a methadone-maintained population with or without comorbid chronic pain. Poster presentation. Scottish Mental Health Research Network Annual Scientific Meeting (2013).

Long-term follow-up of core outcome measures in an opioid-dependent treatment-seeking population with or without comorbid chronic pain. Department of Psychiatry Seminar Series, University of Dundee (2014).

Problematic substance use in a methadone-maintained population with or without comorbid chronic pain. Poster presentation. Scottish Pain Research Community Annual Scientific Meeting (2014).

Clinical predictors of illicit drug use associated with chronic pain in treatment-seeking, opioid-dependent patients. Poster presentation. School of Medicine Postgraduate Research Student Symposium (2014).

Three-year risk of emergency healthcare utilisation in a treatment-seeking, opioid-dependent population with comorbid chronic pain. Poster presentation. Scottish Mental Health Research Network Annual Scientific Meeting (2014).

Illicit and non-medical use of substances in a treatment-seeking opioid-dependent population with comorbid chronic pain. Poster presentation. College of Medicine, Dentistry and Nursing Annual Symposium, University of Dundee (2014).

Three-year risk of emergency department attendance in a treatment-seeking, opioid-dependent population with comorbid chronic pain. Oral presentation. 17th Annual Conference of the International Society of Addiction Medicine (2015).

Association between depressive disorders and long-term physical health outcomes in a methadone-maintained treatment population with comorbid chronic pain. Poster presentation. Scottish Mental Health Research Network Annual Scientific Meeting (2015).

Three-year risk of emergency department attendance in a treatment-seeking, opioid-dependent population with comorbid chronic pain. Oral presentation. Scottish Pain Research Community Annual Scientific meeting (2015).

Assessment of treatment outcomes associated with comorbid chronic pain in a methadone-maintained clinical population. Oral presentation. Division of Neuroscience Seminar Series, University of Dundee (2016).

Association between depressive disorders and long-term physical health outcomes in a methadone-maintained treatment population with comorbid chronic pain. Poster presentation. Scottish Pain Research Community Annual Scientific meeting (2016).

Using informatics research methods to validate patient-reported illicit substance use in a methadone-maintained treatment population. Poster presentation. Scottish Mental Health Research Network Annual Scientific Meeting (2016).

Incidence of iatrogenic opioid dependence/abuse following opioid analgesic treatment: A meta-analysis. Oral presentation. School of Medicine Postgraduate Research Student Symposium (2017).

Validation of patient-reported illicit substance use: Correlations between self-reports and urinalysis. Oral presentation. Division of Neuroscience Seminar Series, University of Dundee (2017).

Glossary

Chronic pain (CP): Studies may use one of three established temporal threshold in identifying chronic pain (3, 6 and 12 months). The empirical studies within the present thesis identified chronic pain as pain that had persisted for at least 12 months.

Iatrogenic opioid dependence/abuse/addiction: A syndrome whereby patients become dependent on, or abuse, opioids following analgesic prescribing for the treatment of pain.

Nonmedical substance use: The use of prescription medication without a prescription, or used more often, or in greater quantities, than is prescribed.

Opioid: Natural, synthetic or semi-synthetic narcotic substance (in contrast to 'opiate', which refers specifically to a natural narcotic substance refined from the opium plant).

Opioid abuse: Illicit or nonmedical use of opioids that impacts negatively on health and functioning. For example, ability to retain employment, to maintain successful relationships, and to refrain from drug use despite negative consequences of that use.

Opioid dependence: Physiological dependence on opioids, characterised by tolerance to opioids and withdrawal effects on cessation of opioid use.

Opioid replacement therapy (ORT): Therapeutic opioid administration, over a prolonged period of time, designed to bring illicit opioid use under control in opioid-dependent individuals.

Opioid-induced hyperalgesia (OIH): Increased pain sensitivity as a consequence of therapeutic or recreational opioid exposure.

Pseudoaddiction: Illicit or nonmedical substance use driven by a desire to control unmanaged pain.

Substance use disorders: A clinical diagnosis relating to substance misuse. Concerning opioids, according to DSM-IV criteria, this could mean either opioid dependence or opioid abuse.

Substance misuse: Illicit or nonmedical use of substances.